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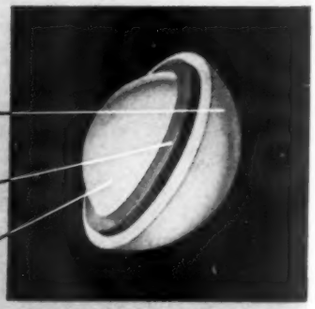
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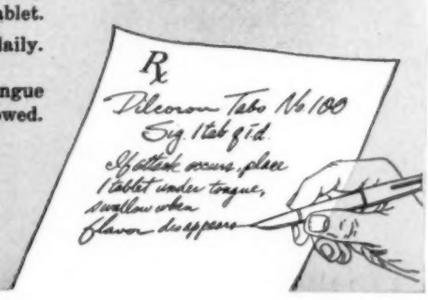


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The American Journal of Medicine

Vol. XXVI MARCH 1959 No. 3

CONTENTS

Editorial

Cardiorespiratory Resuscitation . . . . . HAMILTON SOUTHWORTH 327

Clinical Studies

Ocular Sarcoidosis . . . . . D. GERAINT JAMES 331

Of 200 patients with sarcoidosis, one or another manifestation of eye involvement developed in fifty. These ocular manifestations took various forms: subacute iridocyclitis (eleven cases), chronic iridocyclitis (nineteen cases), phlyctenular or non-specific conjunctivitis (eight cases), keratoconjunctivitis (seven cases), conjunctival follicles, periphlebitis retinas and cataract. Each of these aspects of ocular sarcoidosis is described informatively and in relation to the over-all development of the disease.

Bronchopulmonary Sarcoidosis. Some Unusual Manifestations and the Serious Complications Thereof FRANK J. TALBOT, SOL KATZ AND MARY JANE MATTHEWS 340

Drawing upon a large experience with sarcoidosis, the authors illustrate with case reports a number of unusual bronchopulmonary manifestations of this protean disorder. These include large nodules in the lung substance, simulating metastatic renal carcinoma or sarcoma; the middle lobe syndrome; honeycomb lungs; diffuse bronchiectasis; dysphagia and Horner's syndrome; massive hemoptysis; and spontaneous pneumothorax with acute dyspnea and shock. There is a running commentary on these and related aspects of the sarcoidosis problem.

A Myopathy of Boeck's Sarcoid . . . . . JOHN COLLINS HARVEY 356

While it remains to be demonstrated that Boeck's sarcoid may exclusively involve the skeletal musculature, the present report points up the fact that muscle may be the only apparent site of the disease, and in such instances may cause such marked myopathy as to simulate progressive muscle dystrophy or polymyositis. Three interesting such cases are described, and others from the literature cited.

Sarcoidosis. An Analysis of Forty-Five Cases in a Large Military Hospital
ELLIS P. SINGER, MAJOR NESTOR M. HENSLER AND PAUL F. FLYNN 364

This is an account of the manifestations of sarcoidosis as encountered in forty-five military personnel. The disorder in this segment of the population is in no way distinctive but there are some interesting features, such as the prevalence of ocular manifestations, restrictive ventilatory defects and epididymitis.

Contents continued on page 5

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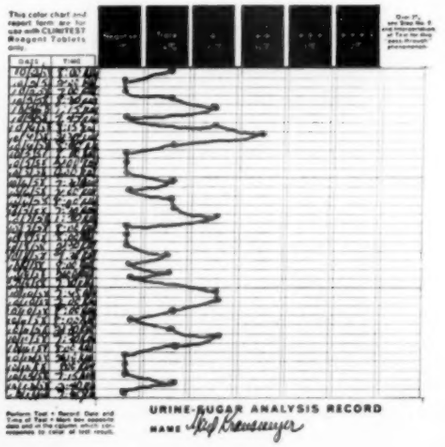
What differentiates "renal diabetes" (renal glycosuria) from diabetes mellitus?

Blood sugar levels. In renal glycosuria they are normal; in untreated diabetes, fasting blood sugars are usually 130 mg.% or over and postprandial levels 170 mg.%, or more.

Source: Joslin, E. P.; Root, H. F.; White, P., and Marble, A.: The Treatment of Diabetes Mellitus, ed. 9, Philadelphia, Lea & Febiger, 1952, pp. 701-702.

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CONTENTS continued–March 1959

VOLUME TWENTY-SIX NUMBER THREE

Tuberculosis-like Disease Caused by Chromogenic Acid-Fast Bacilli
MAJOR NESTOR M. HENSLER, CAPT. PAUL FLANAGAN AND EDITH M. SPRAGUE 376

This report adds five cases of tuberculosis-like disease, due to a chromogenic acid-fast bacillus, to the reports of the past five years. The clinical and pathological picture of the disease produced by these organisms is entirely like that produced by M. tuberculosis. Special bacterial culture studies are required.

Mechanics of Respiration in Bronchial Asthma . . . . . ROE E. WELLS, JR. 384

Careful analysis of the mechanics of breathing in asthmatic patients revealed marked increase in airway resistance and reduction in pulmonary compliance. Of unusual interest is the author's demonstration that inspiratory airway resistance may be almost as high as the expiratory resistance. Indeed therapy often resulted in greater improvement in the former. Evidence is also presented for a "check valve" mechanism, as has been previously reported in emphysema. The findings also indicate an increased work of breathing. The therapeutic implications are discussed in the light of these physiological alterations.

Search for a Neuromuscular Blocking Agent in the Blood of Patients with Myasthenia Gravis . . . . . W. L. NASTUK, A. J. L. STRAUSS AND K. E. OSSERMAN 394

The cause(s) of myasthenia gravis being still unknown, the pathogenesis is currently under intensive study. One of the most intriguing possibilities is that of a circulating curariform agent, a possibility here searchingly investigated by meticulous technics using the frog nerve-muscle preparation. With some exceptions which require further analysis, the method of testing employed gave negative results for the presence of such a curare-like substance in the blood of patients with myasthenia gravis; contrary results by prior investigators are shown to be open to question on experimental grounds. These negative results, as the authors point out, do not altogether exclude the role of a curariform agent in at least some patients with myasthenia gravis but they emphasize the difficulties in demonstration of such a compound.

Plasma Catechol Amine and Electroencephalographic Responses to Acute Postural Change. Evidence of a Deficient Pressor Amine Response in Postural Hypotension
ROGER B. HICKLER, ROE E. WELLS, JR., H. RICHARD TYLER AND JAMES T. HAMLIN, III 410

In normal subjects, tilting produces a significant rise in blood epinephrine and norepinephrine levels accompanied by a normal hemodynamic response. In four of ten normal subjects this response was succeeded by a vasodepressor type of syncope. In four cases of postural hypotension there was no increase in catechol amine levels with concomitant falls in blood pressure. Norepinephrine release could be well correlated with alterations in arteriolar tone as reflected in diastolic blood pressure changes. Hypotensive changes on tilting may be accompanied by electroencephalographic alterations (localized slowing if cerebrovascular disease is present and diffuse slowing in the absence of such disease). These studies help to characterize and to define the group of syncopal syndromes which are being increasingly recognized.

Contents continued on page 7

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References: 1. Crunk, G. A.; Naumann, D. E., and Casson, K.: Antibiotics Annual 1957-1958, New York, Medical Encyclopedia Inc. 1958, p. 397 • 2. Newcomer, V. D.; Wright, E. T., and Sternberg, T. H.. Antibiotics Annual 1954-1955, New York, Medical Encyclopedia Inc., 1955, p. 686.

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CONTENTS continued – March 1959

VOLUME TWENTY-SIX NUMBER THREE

Studies of Acute Rheumatic Fever in the Adult. I. Clinical and Laboratory Manifestations in Thirty Patients . . . ELMER PADER AND SAMUEL K. ELSTER 424

Prevailing diagnostic criteria in acute rheumatic fever, as codified in the Jones criteria, seem to be based largely upon the manifestations of the disease as observed in children. Whatever merit a tallying of pluses and minuses may have in making the diagnois in children is lost when applied to adults, as this study shows, because the diagnostic problems posed are quite different. The authors make clear that acute migratory polyarthritis (of itself of more varied etiology) occurs more frequently than acute carditis, and that such manifestations as subcutaneous nodules, chorea and erythema marginatum are rare. The incidence of prior attacks of rheumatic fever, and therefore of rheumatic heart disease, is of course higher, which also makes interpretation of murmurs, fever and the like more difficult. Nevertheless, acute rheumatic fever is no rarity after the age of puberty, even in the third and fourth decades, and the diagnosis should be made promptly so that appropriate therapy can be instituted without undue delay.

Review

Kuru. Clinical, Pathological and Epidemiological Study of an Acute Progressive Degenerative Disease of the Central Nervous System among Natives of the Eastern Highlands of New Guinea . . . . D. C. GAJDUSEK AND V. ZIGAS 442

This is a report of unusual interest describing a newly discovered disease, of unknown pathogenesis, occurring among the Fore group of New Guinea, and without any apparent counterpart in the Western world. Adult women are principally affected by this neurological disorder, which is characterized by ataxia, tremors and disturbances of affect leading to progressive incapacity and almost invariably to death usually within a year of onset of symptoms. The authors give a detailed account of the clinical, pathological and epidemiological features of Kuru as observed in 200 cases. No etiological agent having been discovered, they conclude that the disease is probably related to the herodofamilial progressive degenerative disorders of the central nervous system. No effective therapy was found.

Seminar on Connective Tissue

Endocrine Control of Connective Tissue . . . . . GUSTAV ASBOE-HANSEN 470

After a brief analysis of the constituents of connective tissue the author proceeds to a consideration of the various endocrine glands and the effects of their hormones upon the several elements of the connective tissue. The discussion begins with the hormones of the hypophysis and adrenals, then thyroid, parathyroid and gonads. Specifically considered further are hormonal effects on tissue regeneration and repair, tumors, infection and inflammation. The next section deals with the more pronounced hormonal effects occurring in hyper- or hypofunction of the endocrine glands, in disease. There is a concluding chapter on the therapeutic use of hormone preparations and the nature of the connective tissue responses.

Contents continued on page 9

THE HEART DISEASE PATIENT NEEDS RELIEF FROM EMOTIONAL STRESS



ANXIETY INTENSIFIES the physical disorder in heart disease. "The prognosis depends largely on the ability of the physician to control the anxiety factor, as well as the somatic disease."

(Friedlander, H. S.: The role of ataraxics in cardiology. Am. J. Cardiol. 1:395, March 1958.)

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(Waldman, S. and Pelner, L.: Management of anxiety associated with heart disease. Am. Pract. & Digest Treat. 8:1075, July 1957.)

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CONTENTS continued–March 1959

VOLUME TWENTY-SIX NUMBER THREE

Clinicopathologic Conference

Multiple Myeloma with Renal Failure 485

Clinicopathologic Conference (Washington University School of Medicine)

Case Report

Chronic Pericardial Effusion in Brothers, with a Note on "Cholesterol Pericarditis"
ABRAHAM GENECIN 496

An interesting report of a puzzling form of chronic pericardial effusion.

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DEWITT STETTEN, JR., M.D.
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Advertising Index on Page 123

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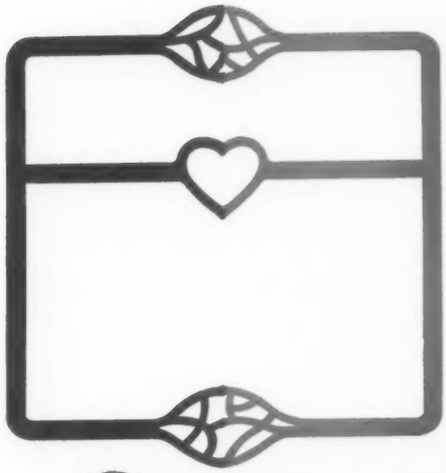
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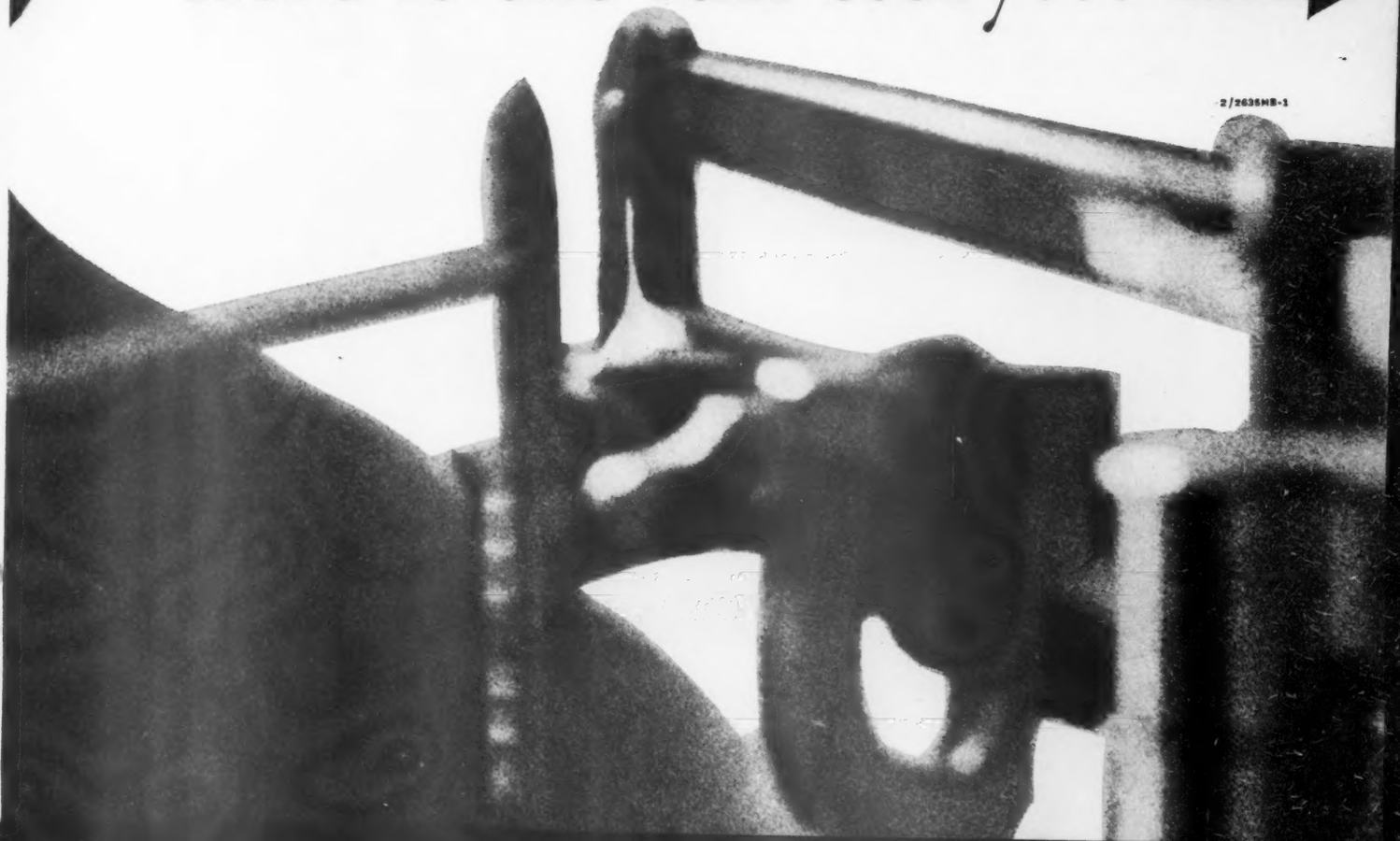


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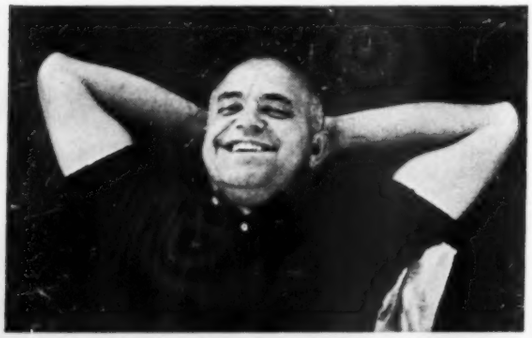
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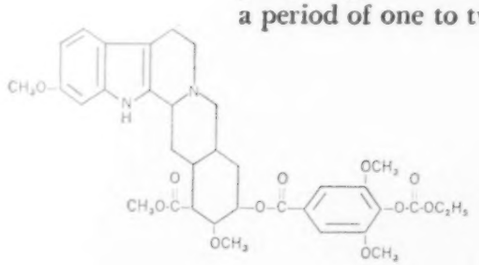
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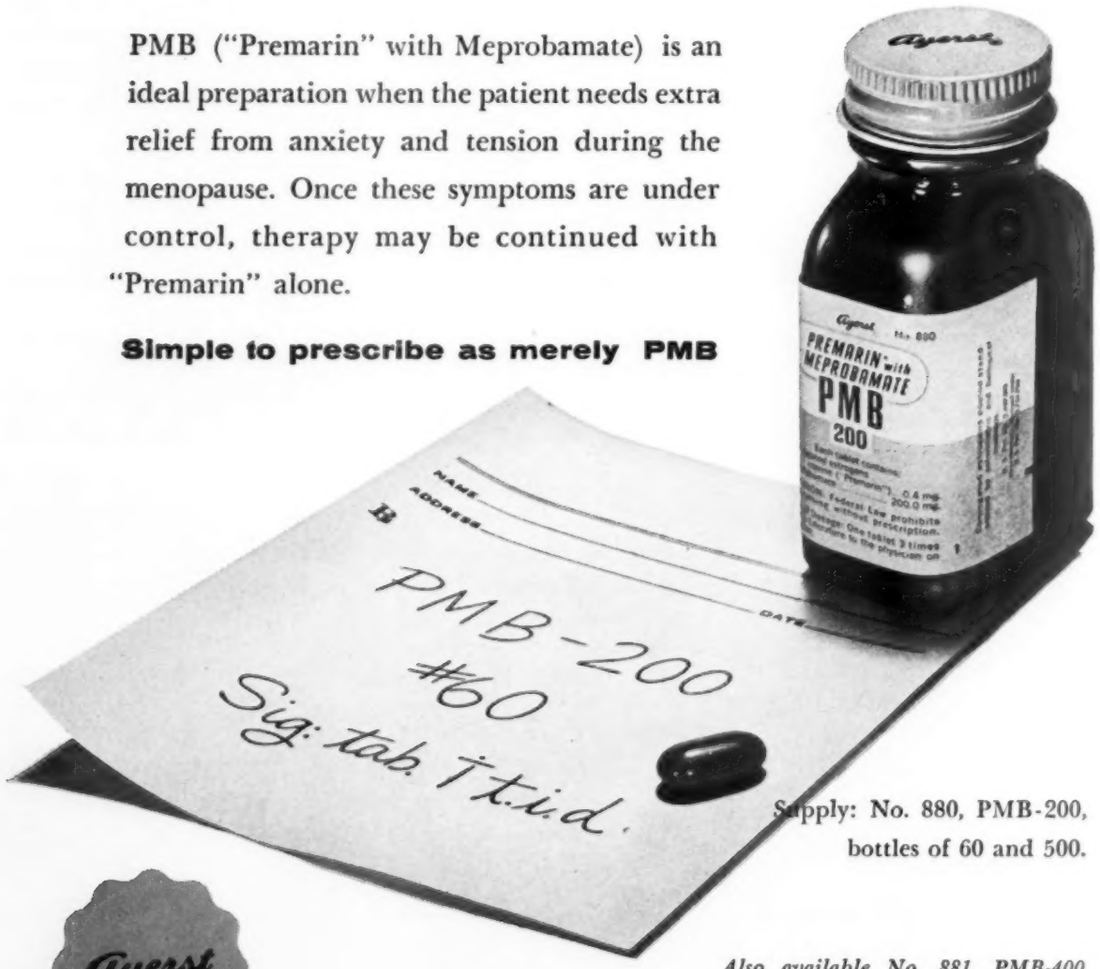
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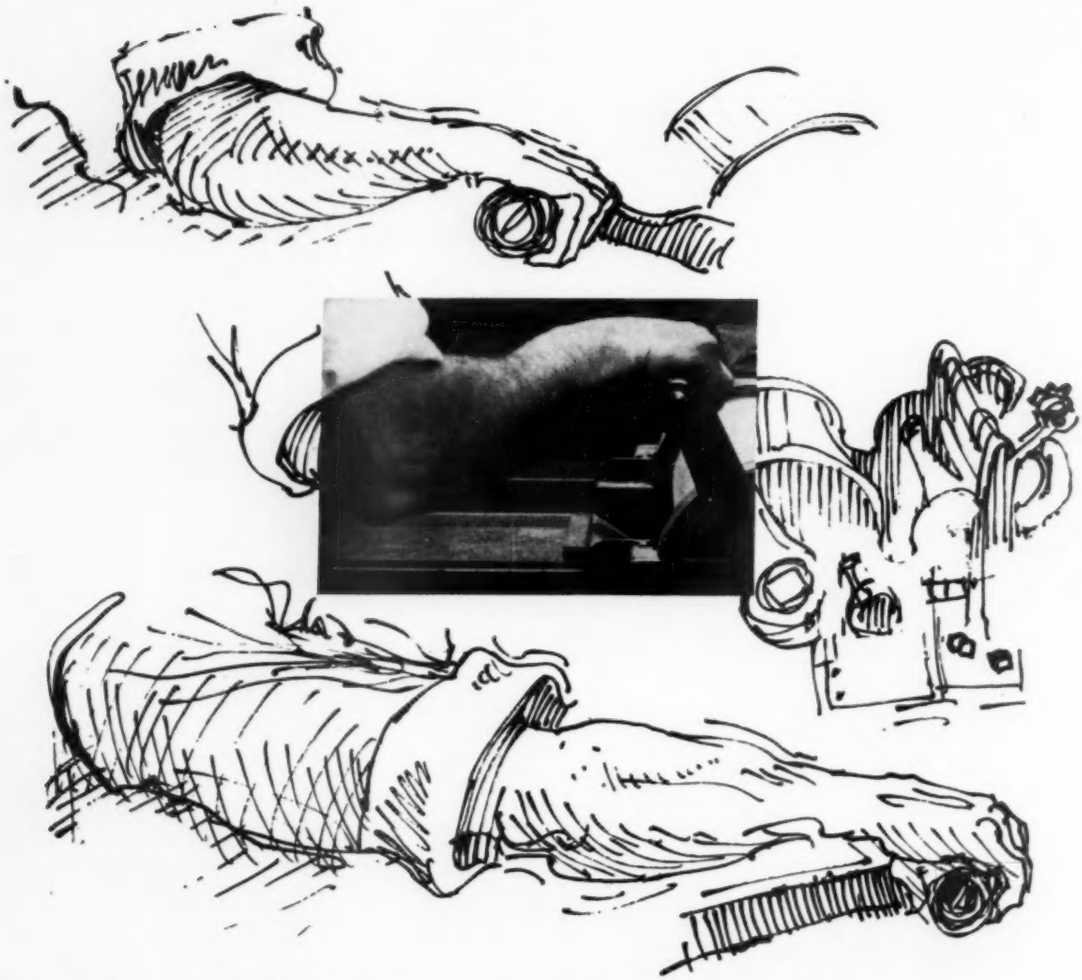
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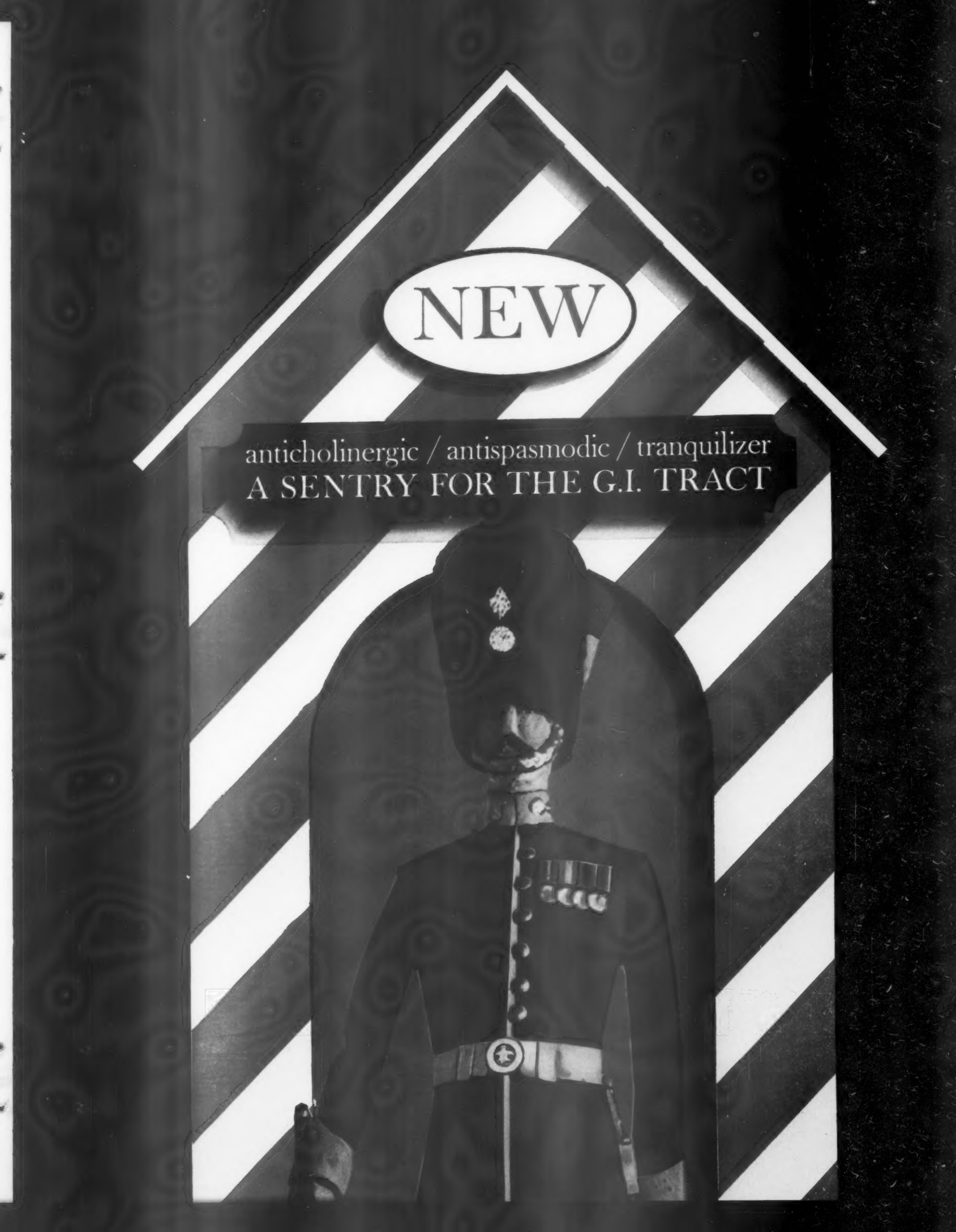
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ENARAX one tablet at breakfast
one tablet at bedtime

full-time relief in

peptic ulcer	gastritis	duodenitis
functional bowel syndrome	gastroenteritis	hiatus hernia (symptomatic)
ulcerative colitis	pylorospasm	genitourinary spasm
biliary tract dysfunctions	cardiospasm	dysmenorrhea

Each ENARAX tablet contains:
Oxyphencyclimine HCl . . . 10 mg.,
Hydroxyzine HCl (ATARAX®) . . . 25 mg.

Dosage: One-half to one tablet twice daily – preferably in the morning and before retiring. The maintenance dose should be adjusted according to therapeutic response. Use with caution in patients with prostatic hypertrophy or glaucoma.

Supplied: In bottles of 60 black-and-white scored tablets.

References: **1.** McHardy, G., et al.: Paper presented at Postgraduate Course in Gastroenterology, University of California School of Medicine, San Francisco, California, January 27, 1958. **2.** Strub, I. H., and Carballo, A.: To be published. **3.** Schuller, E.: Gaz. des Hôpitaux *10*:391 (Apr. 10) 1957. **4.** Farah, L.: Internat. Rec. Med. *169*:379 (June) 1956. **5.** La Barre, J.: Compt. rend. Soc. Biol. (Paris) *150*:1807 (Oct.) 1956. **6.** Harrisson, J. W. E., et al.: Paper presented at the 4th Pan-American Congress of Pharmacy and Biochemistry, Washington, D. C., November 3-9, 1957. **7.** Data in Roerig Medical Department files.

ROERIG Rx

New York 17, N. Y.
Division, Chas. Pfizer & Co., Inc.
Science for the World's Well-Being

RAX



A SENTRY FOR THE G.I. TRACT

look
for this
symbol



SQUIBB

Squibb Quality–the Priceless Ingredient

A workhorse "mycin" for common infections



respiratory infections

prompt, high blood levels

consistently reliable and reproducible blood levels

minimal adverse reactions

With well-tolerated CYCLAMYCIN, you will find it possible to control many common infections rapidly and to do so with remarkable freedom from untoward reactions. CYCLAMYCIN is indicated in numerous bacterial invasions of the respiratory system—lobar pneumonia, bronchopneumonia, tracheitis, bronchitis, and other acute infections. It has been proved effective against a wide range of organisms, such as pneumococci, H. influenzae, streptococci, and many strains of staphylococci, including some resistant to other "mycins." Supplied as Capsules, 125 and 250 mg., vials of 36; Oral Suspension, 125 mg. per 5-cc. teaspoonful, bottles of 2 fl. oz.

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BEFORE IT BEGINS

IMMEDIATE ACTION: KONAKION is a potent, prompt-acting synthetic vitamin K_1 (not an analog) which duplicates the physiologic activity of the natural vitamin.

MULTIPLE CHOICE OF ROUTES OF ADMINISTRATION: oral, intramuscular, or intravenous . . . compatible with most I.V. vehicles, including isotonic saline solution, the usual dextrose solutions in distilled water or in saline, and Ringer's solution.

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in **LOW BACK PAIN**

TORTICOLLIS

BURSITIS and

ANXIETY STATES

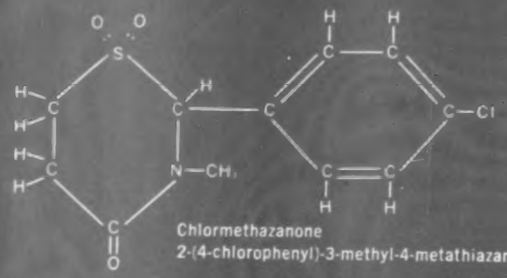
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***as a* TRANQUILIZER**



Chlormethazanone
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Unrelated chemically to any other therapeutic agent in current use. Better tolerated and safer than older drugs.

for clinical results in 4092 patients *see inside*

Trancopal

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*TRANQUILAXANT**

***Potent* MUSCLE RELAXANT**
***and equally effective as a* TRANQUILIZER**

clinical results in 4092 patients[5]

***tran-qui-lax-ant** (tran'kwi-lak'sant)
[< L. tranquillus, quiet; L. laxare, to loosen, as the muscles]

Clinical Comments

"We have just started using it [Trancopal] for relaxing spastic musculature and are *very much encouraged.*"[1]

Baker, University of Minnesota Medical School

"Chlormethazanone [Trancopal] not only relieved *painful muscle spasm,* but allowed the patients to resume their normal activities with no interference in performance of either manual or intellectual tasks."[2]

Lichtman, New York Polyclinic Medical School and Hospital

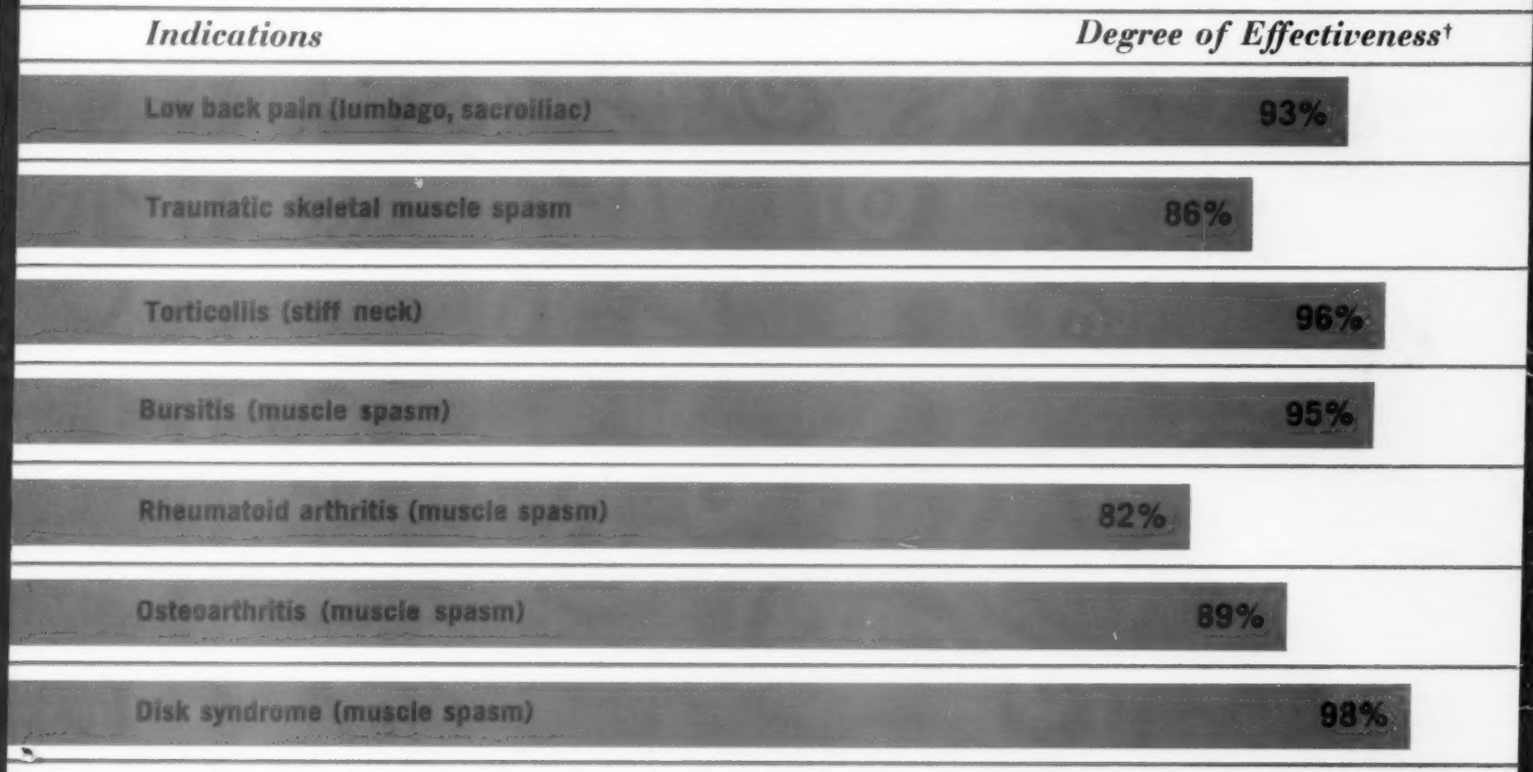
"The effect of this preparation in these cases [skeletal muscle spasm] was *excellent and prompt . . .*"[3]

Mullin and Epifano, Long Island College Hospital

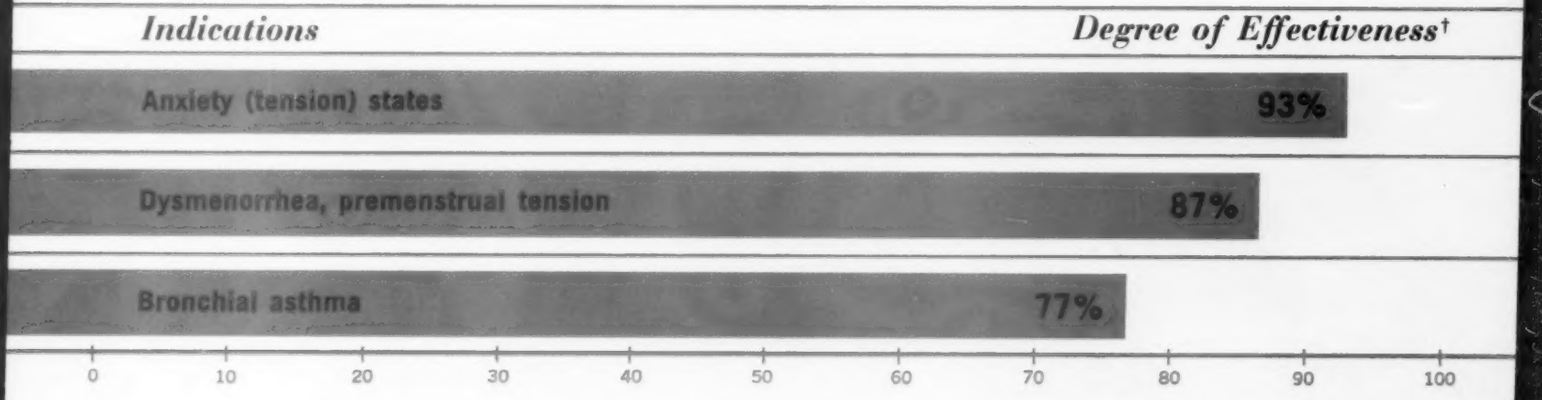
"In 120 patients with *anxiety or tension states,* 114 received satisfactory control of their condition. *Severe dysmenorrhea* and *premenstrual tension* in 65 patients refractory to the usual medications were relieved satisfactorily in 56."[4]

Lichtman

91% Effective in Musculoskeletal Disorders



89% Effective in Psychogenic Disorders



†*Excellent, good and fair*

The results of clinical studies of over 4092 patients by 105 physicians demonstrate that Trancopal often is effective when other drugs have failed. From these studies it is clear that Trancopal probably can provide more help for a greater number of tense, spastic, and/or emotionally upset patients than any other pharmaceutical agent in current use.

Dosage:
Usual adult dose, 1 Caplet (100 mg.) three or four times daily. Children (from 5 to 12 years), ½ Caplet (50 mg.) three or four times daily.

Supplied:
Trancopal Caplets® (peach colored, scored) 100 mg., bottles of 100 and 1000.



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***as a* TRANQUILIZER**

ADVANTAGES OF TRANCOPAL

- Lower incidence of side effects than with zoxazolamine, methocarbamol or meprobamate.
- No known contraindications. Blood pressure, pulse rate, respiration and digestive processes unaffected by therapeutic dosage. No effects on hematopoietic system or liver and kidney function.
- Low toxicity.
- No gastric irritation. Can be taken before meals.
- No clouding of consciousness, no euphoria or depression.
- No perceptible soporific effect, even in high dosage.

INDICATIONS

Musculoskeletal
Low back pain (lumbago)
Neck pain (torticollis, etc.)
Bursitis
Rheumatoid arthritis
Osteoarthritis
Disk syndrome
Fibrositis
Joint disorders (ankle sprain, tennis elbow, etc.)
Myositis
Postoperative myalgias

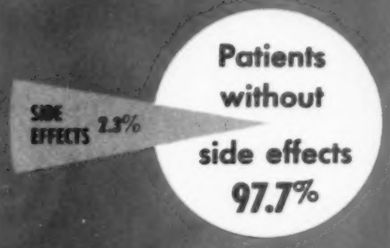
Psychogenic
Anxiety and tension states
Dysmenorrhea
Premenstrual tension
Asthma
Angina pectoris

Neurologic
Muscle spasm (in paralysis agitans, multiple sclerosis, hemiplegia, cerebral palsy)

SAFETY



Comparative pharmacologic tests showed that Trancopal is up to thirteen times as safe, or up to thirteen times less toxic. The measure of safety was the LD_{50} in mice/usual human dose.



INCIDENCE OF SIDE EFFECTS WITH TRANCOPAL IN 4262 PATIENTS.

SUPPLIED

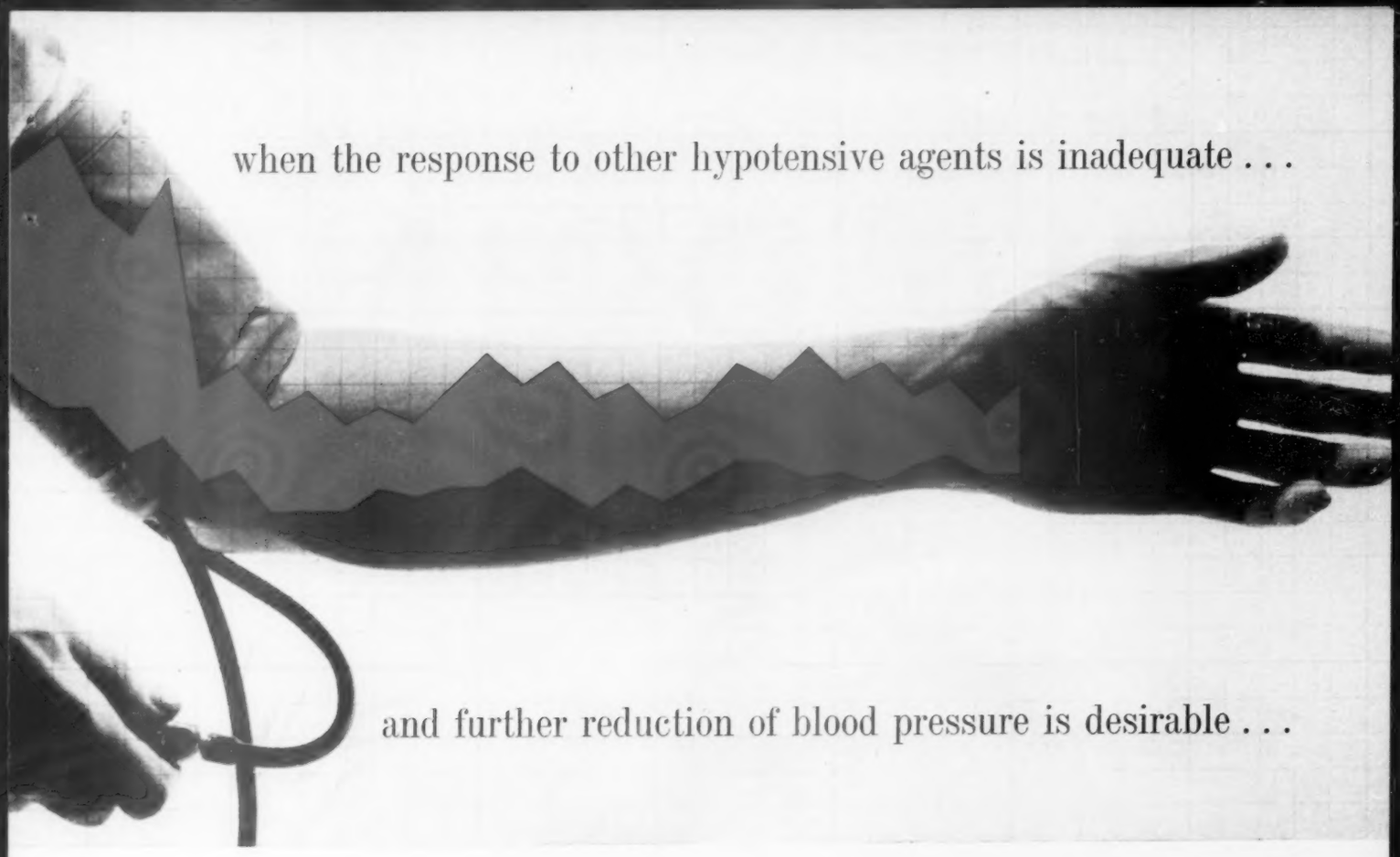
Trancopal Caplets (peach colored, scored) 100 mg., bottles of 100 and 1000.

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Winthrop Laboratories • New York 18, N. Y.

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when the response to other hypotensive agents is inadequate . . .

and further reduction of blood pressure is desirable . . .

adding ganglionic-blocking

INVERSINE®

MECAMYLAMINE HCl

often makes possible a lessening of cardiovascular-renal damage, regression of the basic disease, and prolongation of life

"unnecessary delay must be avoided in establishing ganglion blockade in severe or malignant hypertension"

Beem, J. R., and Moyer, J. H.: Geriatrics 13:378, June 1958.

relieve high blood pressure and its manifestations

INVERSINE®

MECAMYLAMINE HCl

for moderate, severe, and malignant hypertension



"When employed under carefully controlled conditions with adequate attention to proper regulation of dosage, mecamylamine ['INVERSINE'] may be expected to reduce blood pressure effectively and to ameliorate various manifestations of hypertensive-cardiovascular disease. These include such symptoms as headache, dizziness, vertigo, hypertensive encephalopathy, cerebral or subarachnoid hemorrhage, retinopathy, cardiac hypertrophy and, in some cases, cardiac decompensation."

A.M.A. Council on Drugs, New and Nonofficial Drugs: Philadelphia, J. B. Lippincott Co., 1958, p. 285

A GREATLY IMPROVED GANGLIONIC BLOCKING AGENT

'INVERSINE'

- of the orally effective blocking agents, only 'INVERSINE' is completely and uniformly absorbed
- because it is uniformly absorbed, 'INVERSINE' provides predictable, reproducible effects with minimal day-to-day fluctuations
- has a gradual onset of effect, reducing the likelihood of sudden drops in blood pressure
- effective in extremely low dosage (orally, 10 mg. 'INVERSINE' is approximately equivalent to 100 mg. pentolinium, 80 mg. chlorisondamine, 1000 mg. hexamethonium)
- has a long duration of action (6 to 12 hours or longer), permitting convenient dosage schedules
- development of tolerance is not as pronounced as with other ganglionic blocking drugs
- effective in many patients who do not respond to other ganglionic blocking drugs

pretreatment with 'Diuril', or 'Diuril' and rauwolfia, enhances therapy with 'Inversine'

"Pretreatment with chlorothiazide ['DIURIL'] and rauwolfia reduces the dosage requirement, augments blood pressure response, and moderates certain of the side effects of ganglion blocking agents. Although such basal therapy is advantageous, unnecessary delay must be avoided in establishing ganglion blockade in severe or malignant hypertension."

Beem, J. R., and Moyer, J. H.: Geriatrics 13:378, June 1958

dosage recommendations for new patients

1. *Initiate therapy with 'DIURIL'*
'DIURIL' is given in a dosage range of from 250 mg. twice a day to 500 mg. three times a day, depending on severity of the hypertension.

2. *Add other agents*
Other drugs (rauwolfia, 'INVERSINE', hydralazine, etc.) are added as necessary and their dosage adjusted according to patient response.

'INVERSINE' is given in the same manner whether used with other drugs or alone. Recommended initial dosage is 2.5 mg. twice a day, preferably after meals. May be increased by 2.5 mg. at intervals of no less than two days until desired response is obtained. In severe or urgent cases, the increments may have to be larger or more frequent, with the largest dose given preferably at noon or in the evening. 'INVERSINE' is extremely potent and should always be titrated according to the patient's orthostatic blood pressure response.

3. *Adjust dosage of all medication*
The patient must be observed frequently and careful adjustment of all agents should be made to determine optimal maintenance dosage.

Precautions: Side effects of 'INVERSINE' are essentially the same as those encountered with other ganglionic blocking agents. At the first sign of constipation, vigorous treatment must be initiated immediately since paralytic ileus may result if constipation is unchecked. Patients should be informed how to cope with postural hypotension should this occur. 'INVERSINE' is contraindicated in coronary insufficiency, organic pyloric stenosis and recent myocardial infarction. Additional information on 'INVERSINE' and 'DIURIL' is available on request.

Supplied: 'INVERSINE', tablets of 2.5 and 10 mg. Bottles of 100.
'DIURIL', tablets of 250 mg. and 500 mg. Bottles of 100 and 1000.

MSD **MERCK SHARP & DOHME,** DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

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now...when treating upper

Madribon

Disease	No. of Patients	Response: Good or Excellent	Response: Poor
Otitis media	72	65	7
Bronchitis	11	10	1
Obstructive laryngotracheitis	3	3	0
Tonsillitis	21	18	3
Cervical adenitis	13	13	0
Purulent rhinitis or sinusitis	19	16	3
Total	139	125	14

From a study by E. H. Townsend and A. Borgstedt[1]

safe "No side reactions to sulfadimethoxine were observed in the entire series of 167 patients."[1] **effective** "Remarkable improvement, characterized by subjective relief and disappearance of inflammatory symptoms, occurred in 107 out of the 111 patients under study."[2] **economical** "In addition to the clinical efficiency attributable to sulfadimethoxine . . . the economy involved in medication with a fast-acting chemotherapeutic agent warrants its early use. . . ."[3]



respiratory infections

The fastest growing antibacterial bibliography:

1. E. H. Townsend and A. Borgstedt, *Antibiotics Annual 1958-1959*, in press. **2.** J. C. Elia, *Antibiotic Med. & Clin. Therapy*, *6*:(Suppl. 1), 1959. **3.** B. H. Leming, Jr., C. Flanigan, Jr. and B. R. Jennings, *Antibiotic Med. & Clin. Therapy*, *6*:(Suppl. 1), 1959. **4.** H. P. Ironson and C. Patel, *Antibiotic Med. & Clin. Therapy*, *6*:(Suppl. 1), 1959. **5.** S. Ross, J. R. Puig and E. A. Zaremba, *Antibiotics Annual 1958-1959*, in press. **6.** J. D. Young, Jr., W. S. Kiser and O. C. Beyer, *Antibiotic Med. & Clin. Therapy*, *6*:(Suppl. 1), 1959. **7.** T. D. Michael, *Antibiotic Med. & Clin. Therapy*, *6*:(Suppl. 1), 1959. **8.** W. A. Leff, *Antibiotic Med. & Clin. Therapy*, *6*:(Suppl. 1), 1959. **9.** B. A. Koechlin, W. Kern and R. Engelberg, *Antibiotic Med. & Clin. Therapy*, *6*:(Suppl. 1), 1959. **10.** R. J. Schnitzer and W. F. DeLorenzo, *Antibiotic Med. & Clin. Therapy*, *6*:(Suppl. 1), 1959. **11.** R. J. Schnitzer, W. F. DeLorenzo, E. Grunberg and R. Russomanno, *Proc. Soc. Exper. Biol. & Med.*, *99*:421, 1958. **12.** W. F. DeLorenzo and R. Russomanno, *Antibiotic Med. & Clin. Therapy*, *6*:(Suppl. 1), 1959. **13.** B. Fust and E. Boehni, *Antibiotic Med. & Clin. Therapy*, *6*:(Suppl. 1), 1959. **14.** W. F. DeLorenzo and A. M. Schumacher, *Antibiotic Med. & Clin. Therapy*, *6*:(Suppl. 1), 1959. **15.** W. P. Boger, *Antibiotics Annual 1958-1959*, in press. **16.** O. Brandman, C. Oyer and R. Engelberg, *J. M. Soc. New Jersey*, *56*:24, Jan. 1959. **17.** J. F. Glenn, J. R. Johnson and J. H. Semans, *Antibiotic Med. & Clin. Therapy*, *6*:(Suppl. 1), 1959.

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MADRIQID[T.M.]
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POSITIVE EVIDENCE THAT "MEDIATRIC" INCREASES MUSCLE STRENGTH

in six weeks' time, left hand grip strength increased from 20 to 52 pounds—nearly doubled in right hand.*



1 KILOGRAM = 2.2 POUNDS

*Patient E. H., male, age 88, started on "Mediatric" July 24, 1952. Right hand grip strength measured 32 pounds, left hand, 20 pounds. Six weeks later, grip strength improved to 62 and 52 pounds, respectively. On June 29, 1954, after continuous therapy both right and left hand grip strength registered 100 pounds.



improved grip strength with steroid-nutritional therapy objectively demonstrated by mechanical tests

Muscle performance in terms of power, endurance, and coordination has been evaluated in a series of patients before and after "Mediatric" therapy.[1] Grip strength measured by dynamometer and tested at periodic intervals showed remarkable improvement — averaging 60 per cent in right hand and more than 100 per cent in left, even in relatively short periods of time. Other musculo-skeletal tests were equally successful.

"Mediatric" contains estrogen and androgen in amounts that will help counteract declining gonadal hormone secretion, maintain a positive nitrogen balance, and promote synthesis of protein in muscle, bone and other tissues.

Combining both steroids and important nutritional supplements such as vitamin C, B_{12}, other B vitamins and ferrous sulfate, "Mediatric" brings about increase in physical strength, overcomes general malaise, easy fatigability, lack of interest and vague pains in the bones and joints. In addition, "Mediatric" improves mental outlook and its general "tonic" effect is of especial benefit to your patient.

"MEDIATRIC"®

STEROID-NUTRITIONAL COMPOUND

each capsule or tablet contains:

STEROIDS	
Conjugated estrogens equine ("Premarin"®)	0.25 mg.
Methyltestosterone	2.5 mg.
NUTRITIONAL SUPPLEMENTS	
Vitamin C (ascorbic acid)	100.0 mg.
Vitamin B_{12} with intrinsic factor concentrate	1/6 U.S.P. Unit
Thiamine mononitrate (B_1)	10.0 mg.
Riboflavin (B_2)	5.0 mg.
Nicotinamide	50.0 mg.
Pyridoxine HCl (B_6)	3.0 mg.
Calc. pantothenate	20.0 mg.
Folic acid U.S.P.	0.33 mg.
Ferrous sulfate exsic.	30.0 mg.
ANTIDEPRESSANT	
d-Desoxyephedrine HCl	1.0 mg.

Suggested Dosages: Male — *1 capsule or 1 tablet daily, or as required.* Female — *1 capsule or 1 tablet daily, or as required, taken in 21 day courses with a rest period of one week between courses.*

Supplied: *Capsules — No. 252 — Bottles of 30, 100, and 1,000. Tablets — No. 752 — Bottles of 100 and 1,000.*

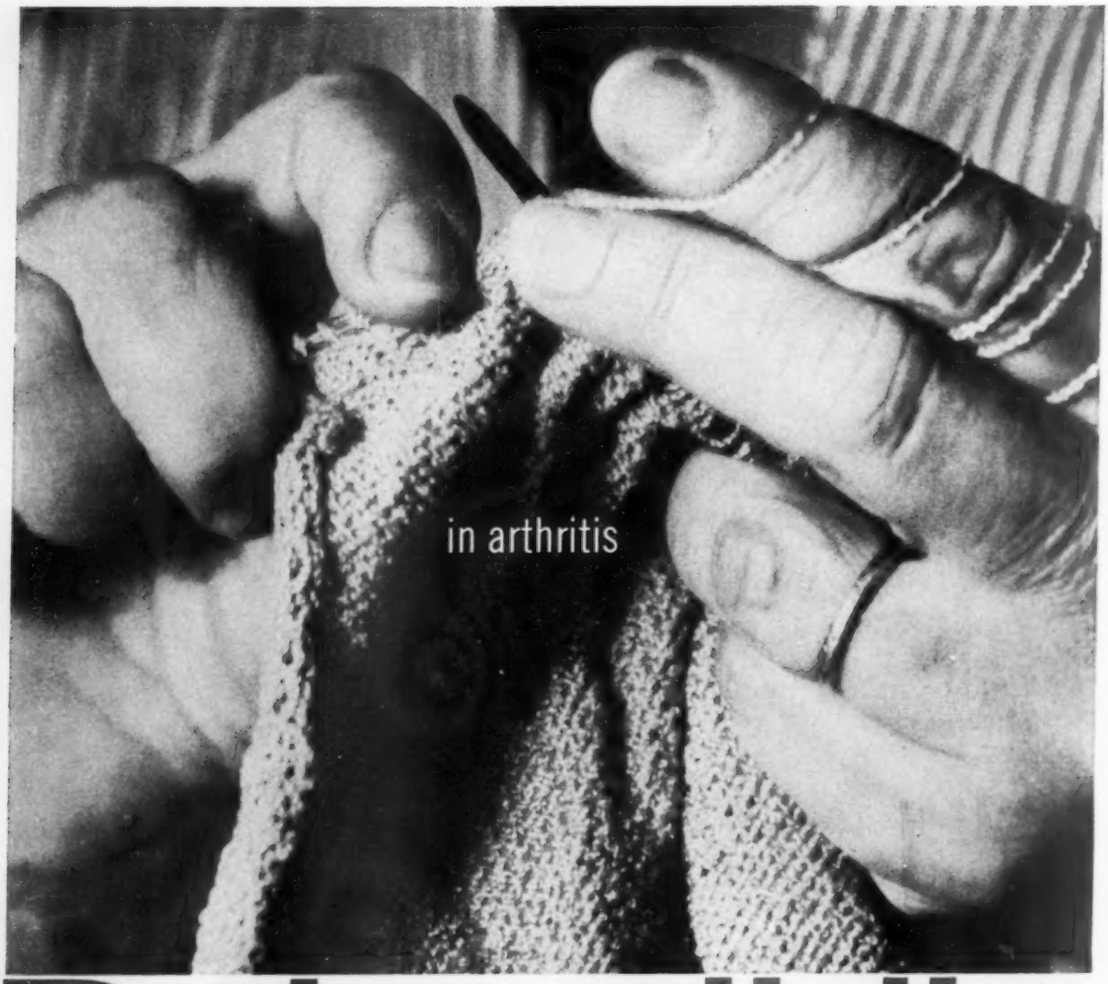
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1. Perlman, R. M., and Dorinson, S. M.: Presented before the Third Congress of the International Association of Gerontology, London, England, July 19-23, 1954.

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Butazolidin®

(phenylbutazone GEIGY)

tablets · alka capsules **potent · nonhormonal · anti-inflammatory agent**

BUTAZOLIDIN tablets or the Alka capsules are **equally effective but individually adaptable in a wide range of arthritic disorders.**

Recent clinical reports continue to justify the selection of Butazolidin for rapid relief of pain, increased mobility, and early resolution of inflammation.

Gouty Arthritis: "...95 per cent of patients experienced a satisfactory response..."[1]

Rheumatoid Arthritis: In "A total of 215 cases...over half, 50.7 per cent showed at least major improvement, with 21.8 per cent showing minor improvement...."[2] **Osteoarthritis:** 301 cases showed "...a total of 44.5 per cent with complete remission or major improvement. Of the remainder, 28.2 per cent showed minor improvement...."[2] **Spondylitis:** All patients "...experienced initial major improvement that was maintained throughout the period of medication."[3] **Painful Shoulder Syndrome:** Response of 70 patients with various forms showed "...8.6 per cent complete remissions, 47.1 per cent major improvement, 20.0 per cent minor improvement...."[3]

References: 1. Graham, W.: Canad. M. A. J. 79:634 (Oct. 15) 1958. 2. Robins, H. M.; Lockie, L. M.; Norcross, B.; Latona, S., and Riordan, D. J.: Am. Pract. Digest Treat. 8:1758, 1957. 3. Kuzell, W. C.; Schaffarzick, R. W.; Naugler, W. E., and Champlin, B. M.: New England J. Med. 256:388, 1957.

Availability BUTAZOLIDIN® (phenylbutazone GEIGY): Red coated tablets of 100 mg. BUTAZOLIDIN® Alka: Capsules containing BUTAZOLIDIN® (phenylbutazone GEIGY), 100 mg.; dried aluminum hydroxide gel, 100 mg.; magnesium trisilicate 150 mg.; homatropine methylbromide, 1.25 mg.

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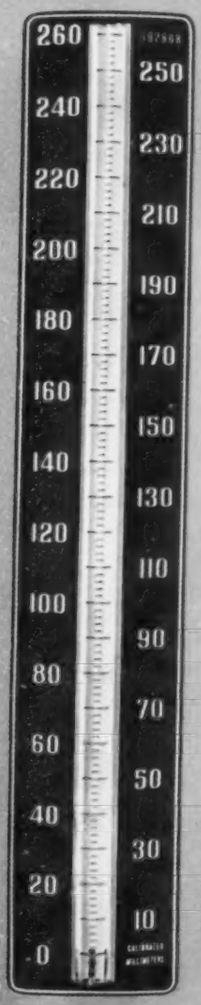
more hypertensives can be better controlled
with **DIUPRES** than with any other agent
... with greater simplicity and convenience

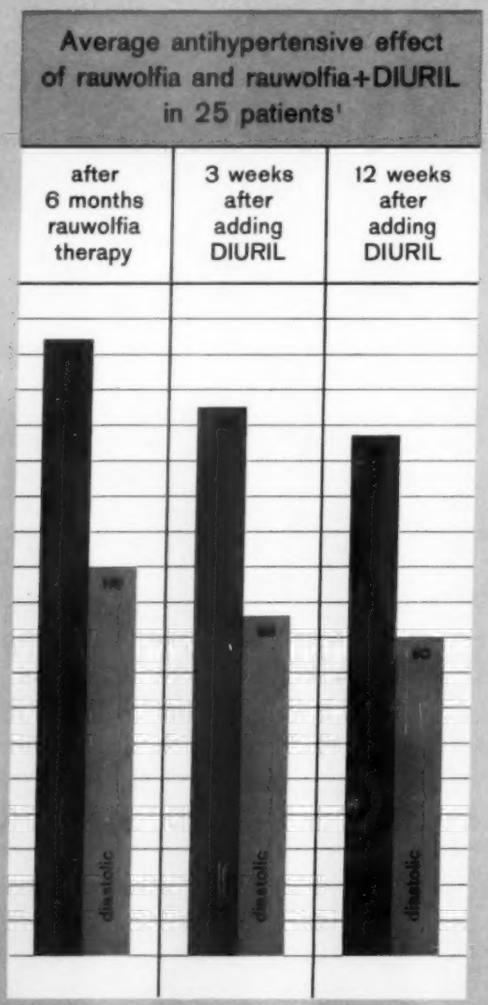
a logical alliance of two antihypertensives
you know and trust provides

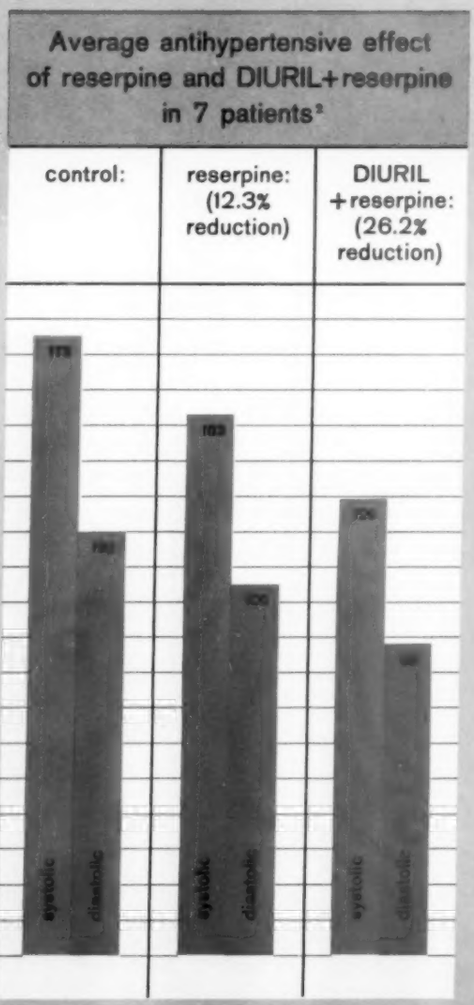
increased effectiveness, decreased side effects

potentiated effect

DIUPRES produces an effect greater than either DIURIL or reserpine alone. It is effective in many patients who respond inadequately or not at all to either DIURIL or reserpine.







DIUPRES

DIURIL® WITH RESERPINE

effective therapy for most patients

DIUPRES by itself usually provides effective therapy for a majority of patients with mild or moderate hypertension, and even for many patients with severe hypertension. Many patients now treated with other agents which frequently cause distressing side effects can be adequately managed with well tolerated DIUPRES.

provides basic therapy

Should other drugs need to be added to DIUPRES, they can be given in much lower than usual dosage so that their side effects are often strikingly reduced.

rapid onset of effect

The antihypertensive action of DIUPRES is rapidly evident. (Considerable time may elapse before the antihypertensive effect of reserpine alone is observed.)

fewer and less severe side effects

DIUPRES may be expected to cause fewer and less severe side effects than are encountered with other antihypertensive therapy. (Since DIURIL and reserpine potentiate each other, the required dosage of each is usually less when given together as DIUPRES than when given alone. Such reduction in dosage makes side effects less likely to occur.)

often obviates weight gain

DIUPRES minimizes the problem of weight gain seen with reserpine (reserpine alone has been reported to produce weight gain in 50 per cent of patients).[1,4]

virtually eliminates fluid retention

DIUPRES is not likely to cause either clinical or subclinical retention of sodium and water. (Hypotensive drugs, particularly rauwolfia[5] and hydralazine,[6] may cause fluid retention. Even when such retention is subclinical, their antihypertensive effectiveness is diminished.[6])

diet more palatable

With DIUPRES, there is less need for rigid restriction of dietary salt, which patients find so burdensome.

> *"It may well be that the drug* [DIURIL] *produces the benefits of a markedly restricted low sodium diet but without its hardships."*[3]

subjective and objective improvement

DIUPRES allays anxiety and tension, thus reducing the emotional component of hypertension. Organic changes of hypertension may be arrested and reversed. Headache, dizziness, palpitations and tachycardia are usually promptly relieved by DIUPRES. When the *anginal syndrome* accompanies hypertension, the administration of DIUPRES may also cause diminution or even disappearance of this syndrome concurrent with control of the hypertension.

convenient, controlled dosage

Instead of two separate prescriptions, you write one prescription . . . the patient takes one tablet, rather than two different tablets . . . and the dosage schedule is easier for the patient to remember and follow.

> *"patients have fewer lapses and make fewer mistakes in dosage, the simpler the regimen can be made. Therefore I do not hesitate to use more than one medicament combined in one tablet, provided this gives approximately the correct dosage of each."*[6]

economical

DIUPRES will cost the patient less than if he were given two separate prescriptions for its components.

Indications:
DIUPRES is indicated in hypertension of all degrees of severity. It can be used in the following ways:

- as total therapy
- as primary therapy, adding other drugs if necessary
- as replacement or adjunctive therapy in patients now treated with other agents

Precautions:
The precautions normally observed with DIURIL or reserpine apply to DIUPRES. Additional information on DIUPRES is available to physicians on request.

Recommended dosage range:
DIUPRES-500—one tablet one to three times a day.
DIUPRES-250—one tablet one to four times a day.
If necessary, other agents may be added.
If the patient is receiving ganglion blocking agents or hydralazine, their dosage should be cut by 50 per cent when DIUPRES is added.



DIUPRES-500

500 mg. DIURIL (chlorothiazide), 0.125 mg. reserpine.
Bottles of 100, 1000.



DIUPRES-250

250 mg. DIURIL (chlorothiazide), 0.125 mg. reserpine.
Bottles of 100, 1000.

the first "wide range" antihypertensive

DIUPRES

DIURIL® WITH RESERPINE

1. Rochelle, J. B., III, Bullock, A. C., and Ford, R. V.: Potentiation of antihypertensive therapy by use of chlorothiazide, *J.A.M.A.* 168:410, Sept. 27, 1958. 2. Freis, E. D., Wanko, A., Wilson, I. M., and Parrish, A. E.: Treatment of essential hypertension with chlorothiazide (Diuril), *J.A.M.A.* 166:137, Jan. 11, 1958. 3. Freis, E. D.: Treatment of hypertension. (Presented at the Annual Meeting of Southern Medical Association, Nov. 13, 1957.) 4. Moyer, J. H., Dennis, E., and Ford, R.: Drug therapy (Rauwolfia) of hypertension, *A.M.A. Arch. Int. Med.* 96:530, Oct. 1955. 5. Perera, G. A.: Edema and congestive failure related to administration of rauwolfia serpentina, *J.A.M.A.* 159:439, Oct. 1, 1955. 6. Wilkins, R. W.: Precautions in use of antihypertensive drugs, including chlorothiazide, *J.A.M.A.* 167:801, June 14, 1958.

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Deprol ► acts promptly to control depression *without* stimulation

► restores natural sleep

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Deprol is unlike amine-oxidase inhibitors

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Composition: Each tablet contains 400 mg. meprobamate and 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl).

Supplied: Bottles of 50 scored tablets.

1. Alexander, L.: Chemotherapy of depression—Use of meprobamate combined with benactyzine (2-diethylaminoethyl benzilate) hydrochloride. J.A.M.A. 166:1019, March 1, 1958. 2. Current personal communications; in the files of Wallace Laboratories.

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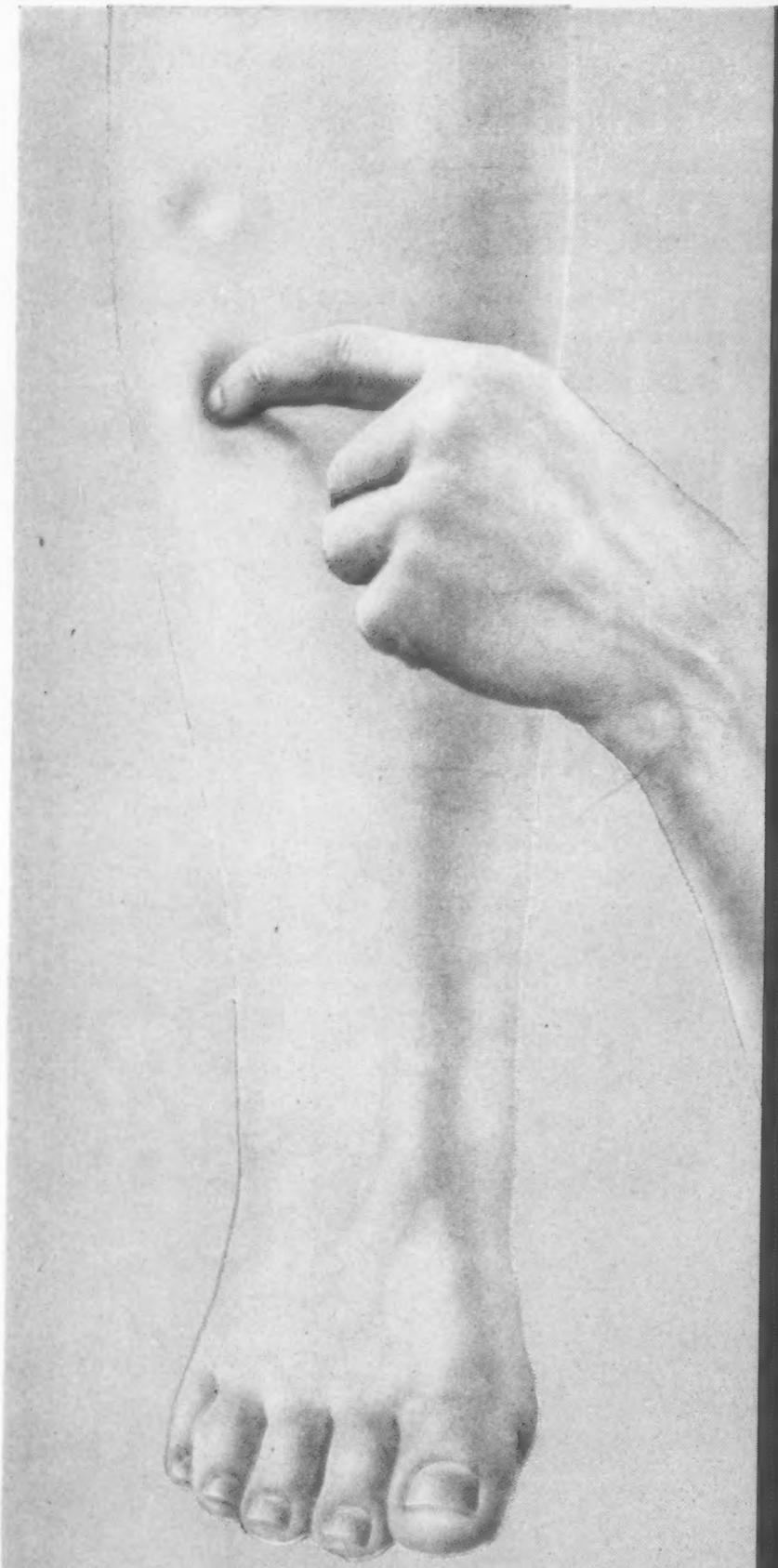
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1. Landes, R. P. and Peters, M.: Postgrad. Med. 23:648, June 1958.

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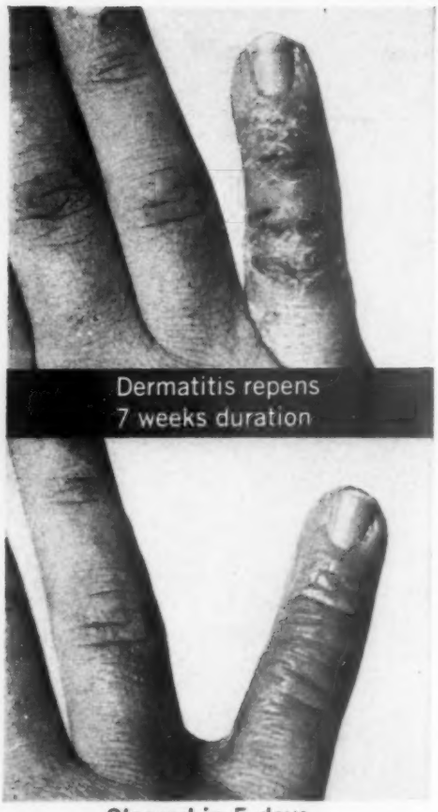
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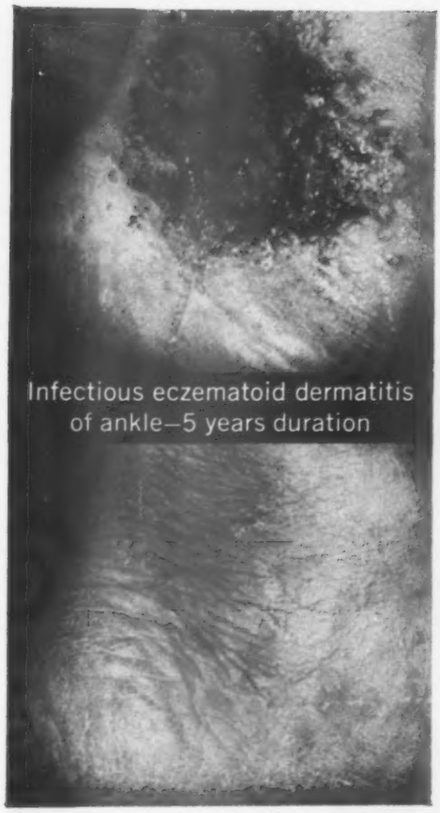
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References: 1. Shelmire, J.B., Jr.: Monographs on Therapy 3:164 (Nov.) 1958. • 2. Nix, T.E., Jr., and Derbes, V.J.: Monographs on Therapy 3:123 (Nov.) 1958. • 3. Robinson, R.C.V.: Bull. School of Med., U. Maryland 43:54 (July) 1958. 4. Sternberg, T.H.: Newcomer, V.D., and Reisner, R. M.: Monographs on Therapy 3:115 (Nov.) 1958. • 5. Clark, R.F., and Hallett, J. J.: Monographs on Therapy 3:153 (Nov.) 1958 • 6. Smith, J.G., Jr.; Zawisza, R. J., and Blank, H.: Monographs on Therapy 3:111 (Nov.) 1958. • 7. Montgomery, R.M.: Monographs on Therapy 3:143 (Nov.) 1958. • 8. Monographs on Therapy 3:137 (Nov.) 1958. 9. Howell, C. M., Jr.: North Carolina M.J. 19:449 (Oct.) 1958. • 10. Bereston, E.S.: South. M. J. 50:547 (April) 1957.

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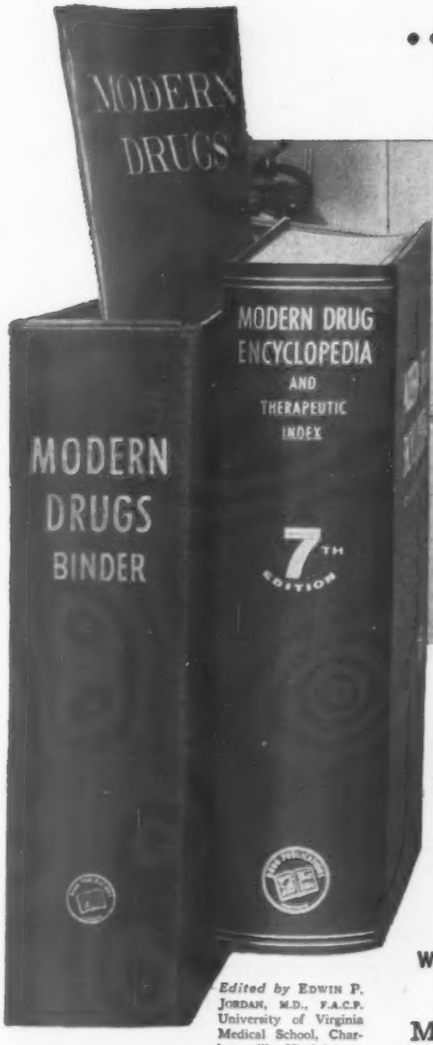
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1. Mulinos, M. G., and Jerry Glass, G. B.: Gastroenterology 24: 385-393 (May-Aug.) 1953.

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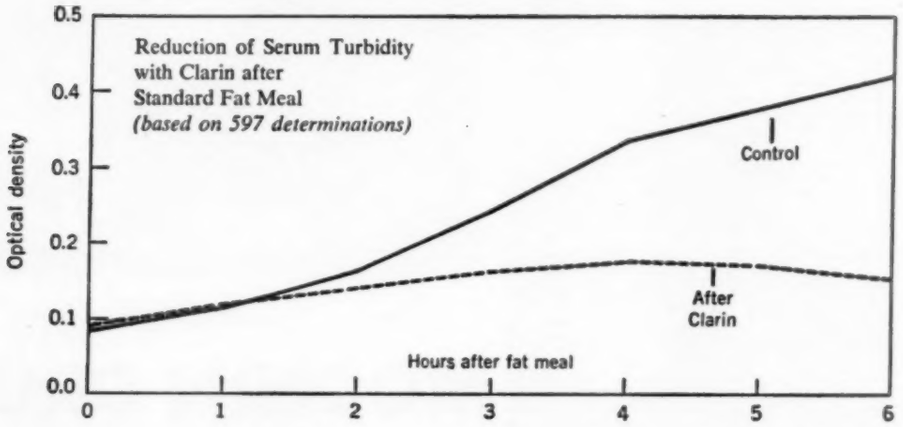
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1. Council on Drugs, J.A.M.A. *166*:52 (Jan. 4) 1958. 2. Hahn, P. F.: Science *98*:19 (July 2) 1943. 3. Fuller, H. L.: Angiology *9*:311 (Oct.) 1958. 4. Rubio, F. A., Jr.: Personal communication. 5. Engelberg, H., *et al.*: Circulation *13*:489 (April) 1956.

*Trade Mark. Patent applied for.

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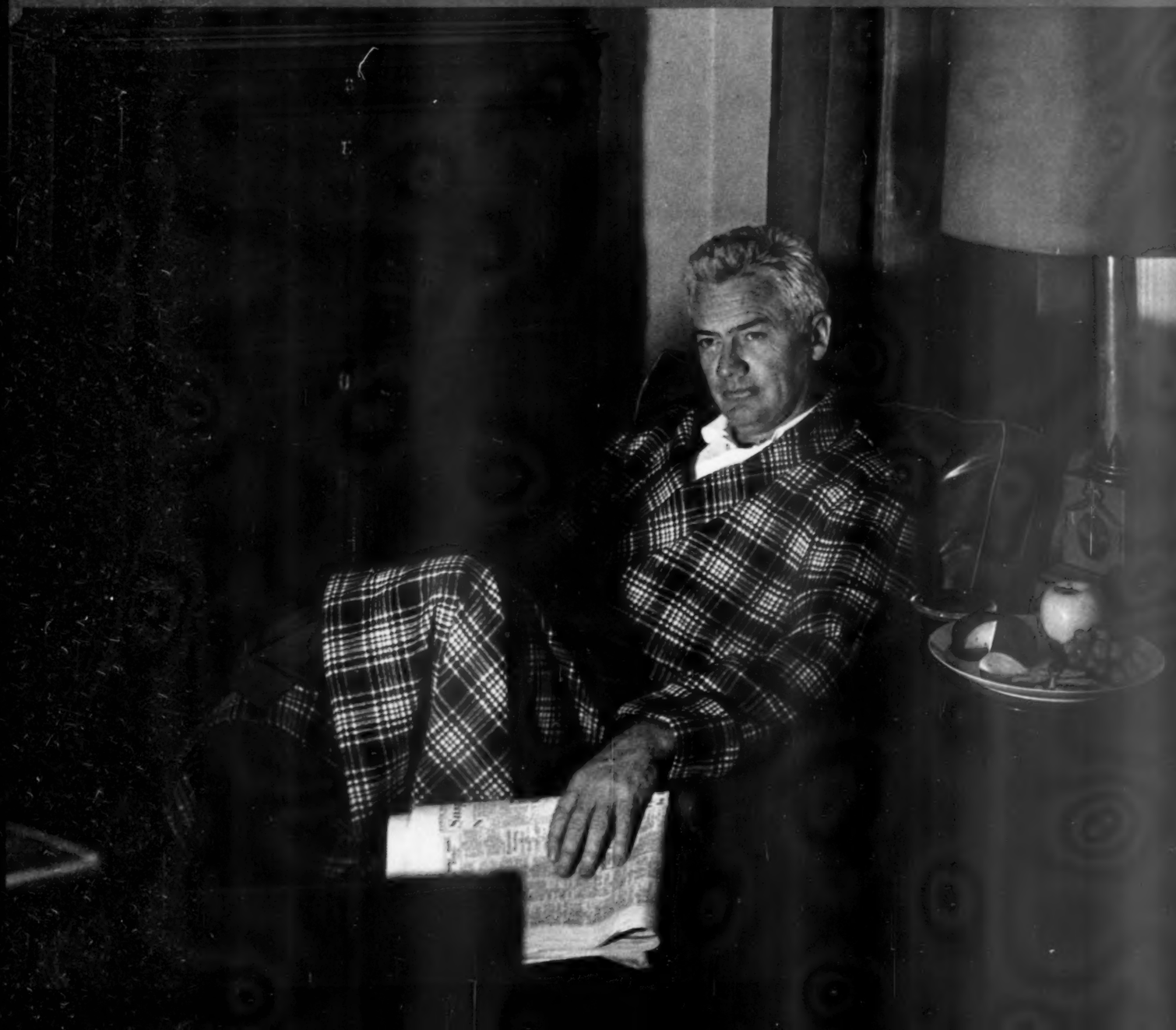
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Current Concepts in Therapy: Sedative-Hypnotic Drugs, N. Engl. J. Med. 262:1179-1184 (June 3) 1960

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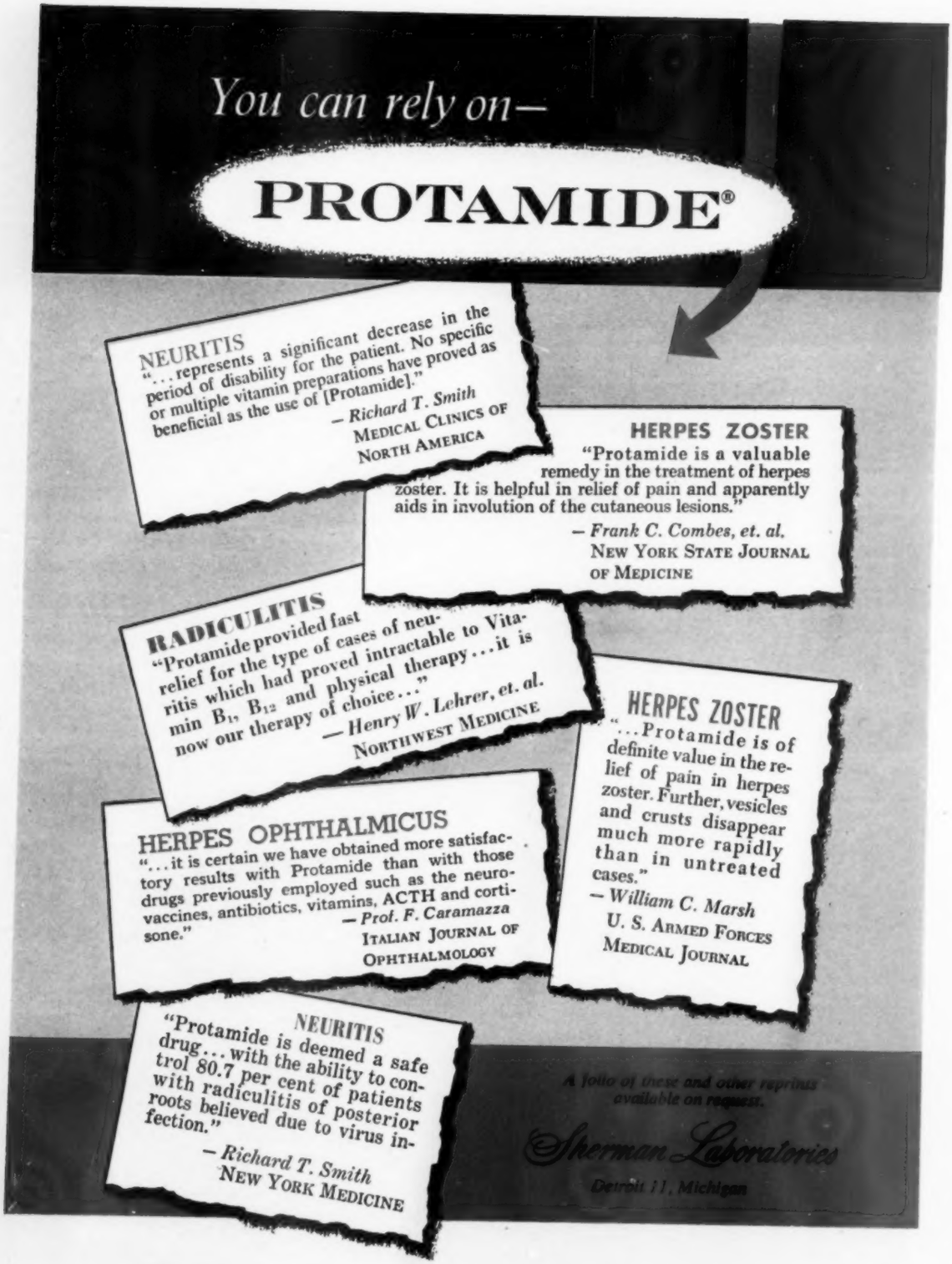
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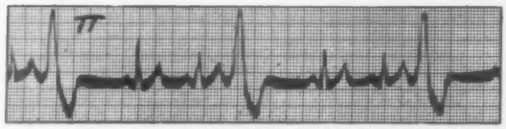
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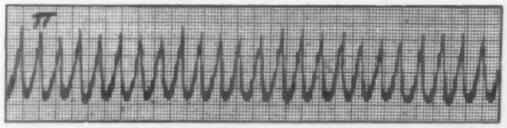
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REFERENCES: 1. Miller, R. F.: Clinical Review, Vol. 1, No. 2 (July) 1958. 2. Van Gasse, J. J.: Clinical Medicine, 5:177-181 (Feb.) 1958. 3. Burrell, Z. L., et al.: Am. J. Cardiol., 1:624 (May) 1958. 4. Hutcheon, D. E., et al.: J. Pharmacol. & Exper. Therap., 118:451 (Dec.) 1956.

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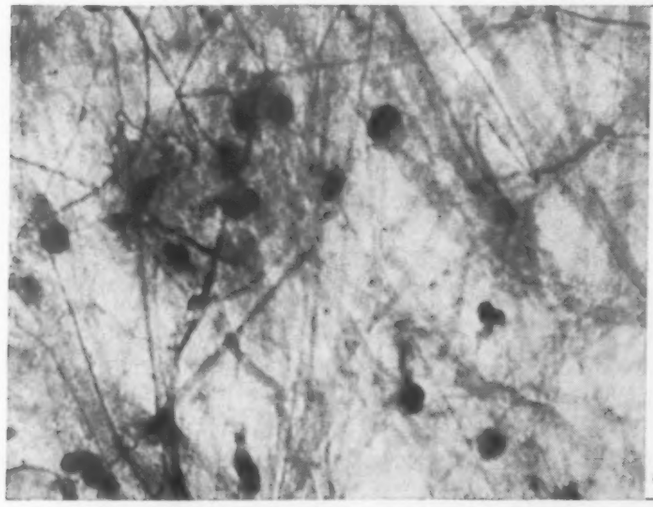
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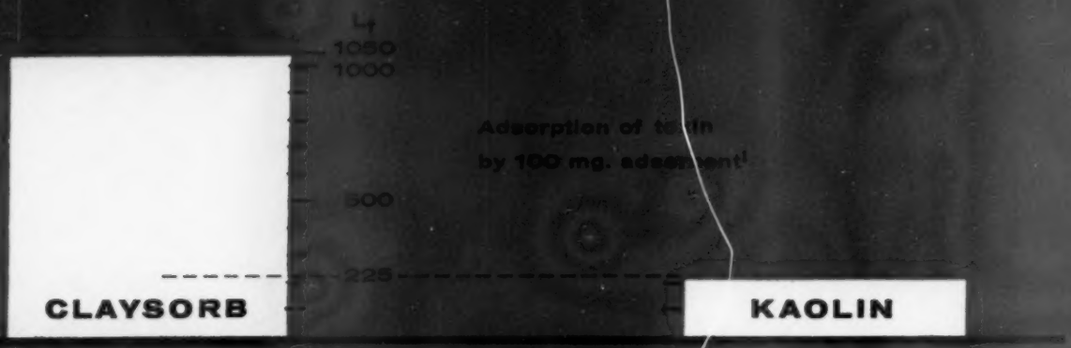
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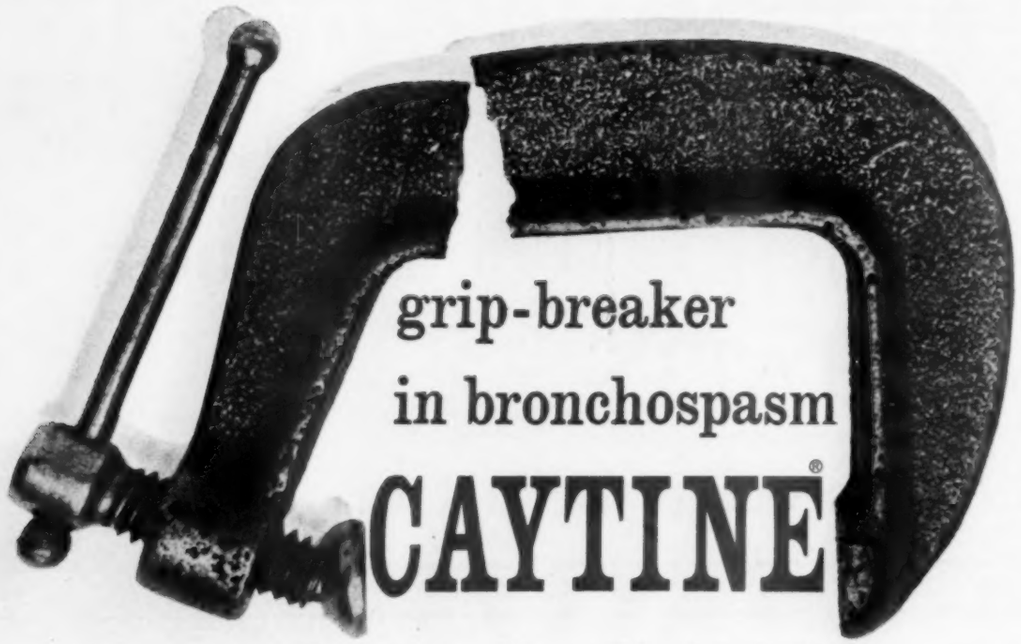
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Drug-induced psychophysiologic depression; physiologic after-effects of certain anesthetics; barbiturate intoxication; moribund states due to systemic infection. (All patients were epileptic, mentally retarded and/or brain damaged.)	"All except two [of 129] patients responded to the initial injection [of parenteral Ritalin] within 1½ to 15 minutes."	"In no instance was there any evidence of untoward effects." ". . . the very poor basic physical condition of our patients in this study, those associated with profound chronic brain damage, accentuates the safety of parenteral Ritalin . . ."[3]

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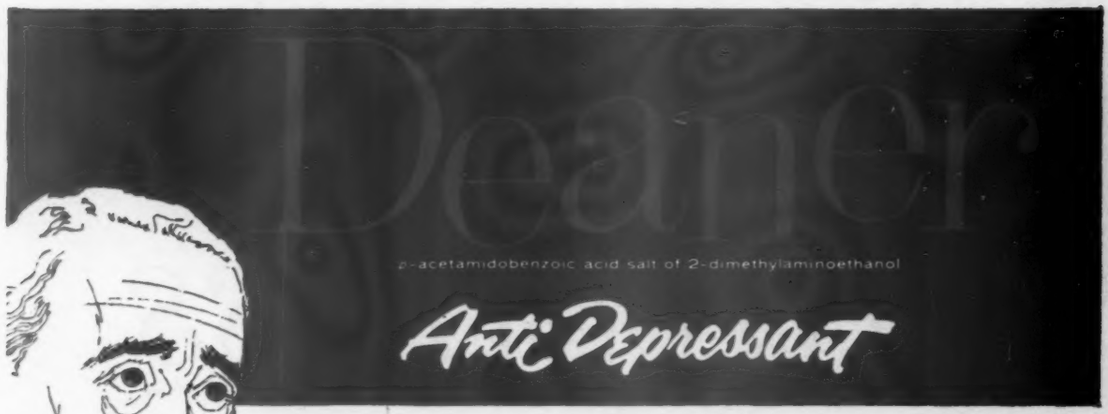
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(1) Leslie, A., and Simmons, D. H.: Am. J. M. Sc. *234*:321, 1957. (2) Settel, E.: Am. Pract. & Digest Treat. *8*:1249, 1957.

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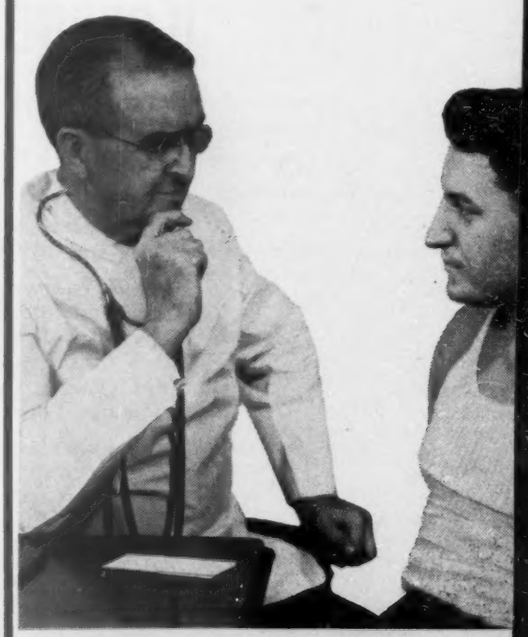
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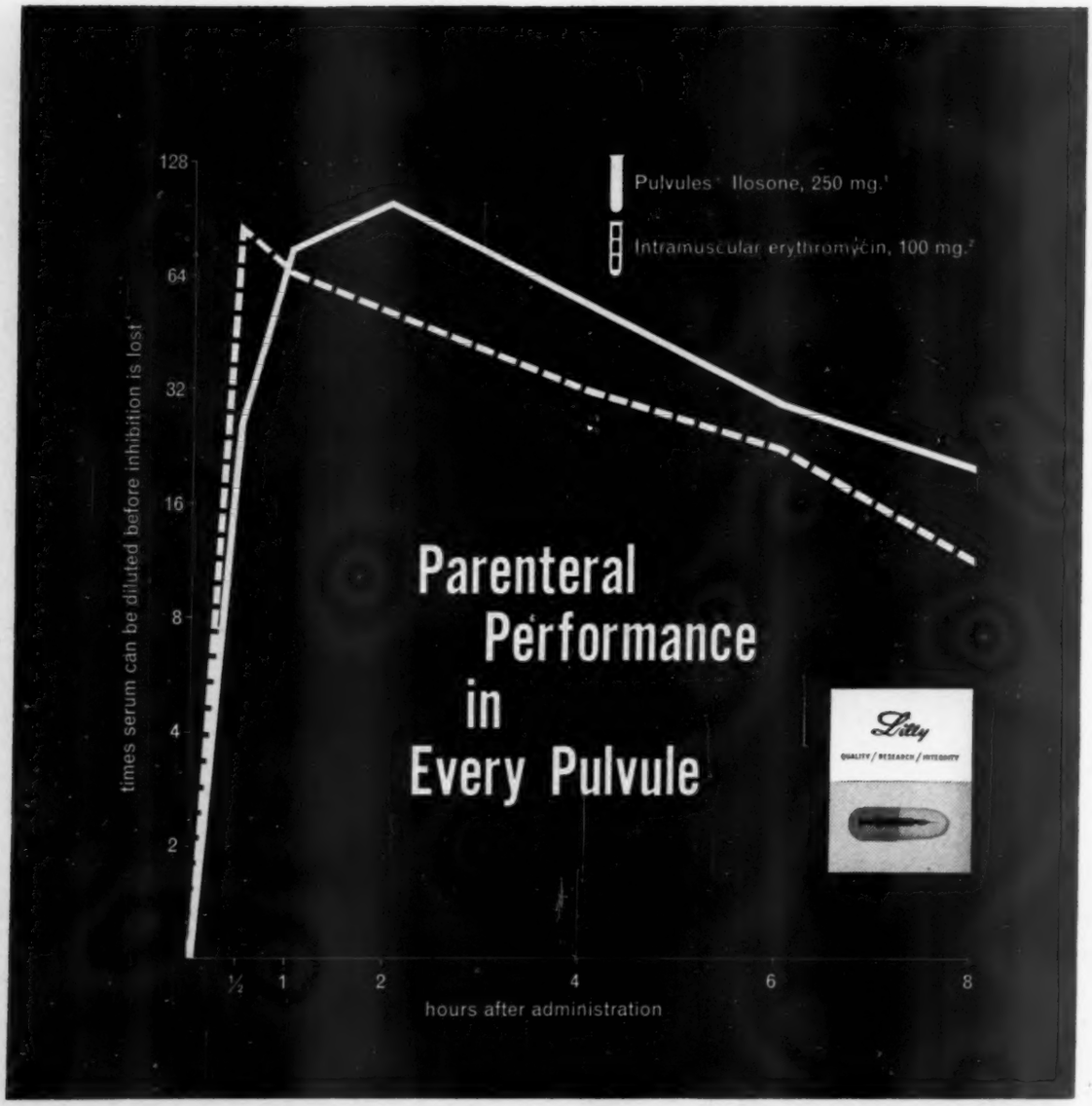


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1. Antibiotic Med. & Clin. Therapy, *5*:609, 1958.

2. Data from Antibiotics Annual, p. 269, 1954-1955.

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Editorial

Cardiorespiratory Resuscitation

For slightly over a decade it has been the accepted procedure, in the rare instance in which cardiac arrest occurs during surgical operations, for the surgeon to open the thorax and institute cardiac massage. Resuscitations may be entirely successful under such circumstances in 75 per cent of cases [*1*]. Starting in 1950, however, reports began to appear in which patients dying suddenly in parts of hospitals distant from the operating room were subjected to emergency thoracotomy with successful restoration of life [*2–8*]. If resuscitation through cardiac massage is at times possible outside the operating room a number of most important questions arise. Under what circumstances should the physician, confronted with a sudden exitus, attempt cardiac massage and when is it wiser for him not to do so? If there are occasions when cardiac massage is indicated outside the operating room, should not the internist, as well as the surgeon, be trained in the technics of cardiorespiratory resuscitation? In considering these problems it is important to realize that the patient is technically dead. Resuscitation therefore involves not the usual efforts to preserve life but the new responsibility of restoring life.

When the physician encounters a case of apparent sudden death he must obviously determine whether or not the heart has really stopped beating and he must decide rapidly. Time lost searching for peripheral pulses or using a sphygmomanometer may make resuscitation impossible. Quick palpation of the abdomen for aortic pulsation is usually most informative if heart sounds are not certainly audible and the general appearance of the patient indicates circulatory arrest.* It is obvious that syncope and shock due to hemorrhage, possibly internal, must be differentiated; specific restorative methods are available for these conditions and

[1] HANKS, E. C. and PAPPER, E. M. Cardiac resuscitation. *New York State J. Med.*, 51: 1801–1814, 1951.

[2] SOUTHWORTH, J. L., MCKUSICK, V. A., PIERCE, E. C., II and RAWSON, F. L., JR. Ventricular fibrillation precipitated by cardiac catheterization: complete recovery of patient after 45 minutes. *J. A. M. A.*, 143: 717–720, 1950.

[3] CELIO, A. Cardiac arrest associated with coronary occlusion: successful resuscitation. *J. Internat. Coll. Surgeons*, 15: 299–304, 1956.

[4] REAGAN, L. B., YOUNG, K. R. and NICHOLSON, J. W. Ventricular defibrillation in patients with probable acute coronary occlusion. *Surgery*, 39: 482–486, 1956.

[5] BECK, C. S., WECKESSER, E. C. and BARRY, F. M. Fatal heart attack and successful defibrillation: new concepts in coronary artery disease. *J. A. M. A.*, 161: 434–435, 1956.

[6] MOZEN, H. E., KATZMAN, R. and MARTIN, J. W. Successful defibrillation of heart, resuscitative procedure started on medical ward and completed in operating room. *J. A. M. A.*, 162: 111–113, 1956.

[7] BROWN, C. D., KNUDSON, J. and SCHROEDER, G. F. Cardiac arrest at work; penknife thoracotomy with recovery. *J. A. M. A.*, 163: 352–353, 1957.

[8] SCHWARTZ, A. and LOBELL, S. M. Cardiac arrest; successful treatment in a patient's room. *J. A. M. A.*, 166: 488–489, 1958.

* If the physician already has an ophthalmoscope in his pocket, a quick look at one fundus may be of value, because beading or segmentation of retinal veins occurs within several seconds of cardiac arrest. Slow forward movement of these beads may, however, continue for over ten minutes after death. A granular pattern also forms in the retinal arteries and within a minute they become empty of blood [*9*].

[9] KEVORKIAN, J. The fundus oculi and the determination of death. *Am. J. Path.*, 32: 1253–1269, 1956.

a false diagnosis of cardiac arrest may be made. It is important to know, if the evidence is immediately available, whether the asystole has been repetitive, as in Stokes-Adams attacks, and whether observations made of the exitus suggest a massive pulmonary embolus or a massive myocardial infarct. Finally the physician must be certain that the precipitating factor has not been laryngeal obstruction.

If the evidence indicates that the heart has actually stopped, the term cardiac arrest may be used and this may be subdivided into cardiac standstill and ventricular fibrillation. Of these standstill is the more common [*10,11*], but hemodynamically there is no difference for neither form of arrest causes any circulation of blood. The physician on the scene cannot make the differentiation without an electrocardiogram or without direct visualization of the heart. There are four courses he can pursue if he elects to try to restart the heart. He can (1) pound on the anterior chest, (2) needle the heart with or without injecting any medication, (3) use an external electric stimulator, and (4) perform a thoracotomy and apply cardiac massage.

When the heart stops there is conclusive evidence that if circulation and oxygenation are not restored within a critical time limit irreparable brain damage almost invariably occurs. This critical limit is generally taken as three to five minutes, a figure borne out by Cole and Corday's review [*12*] of 132 cases of attempted resuscitation, of which all thirty-three that resulted in complete recovery were initiated within four minutes of the arrest.*

Human beings resuscitated after the critical time is past may remain disoriented, comatose, or even decerebrate. Happily such mentally mutilated persons rarely survive for long periods, if they revive at all, but some live on for weeks, months or even years. No physician wants to bring back to life such a person and few would wish to attempt to restore life if the danger of such a travesty was considerable.

The first point to emphasize is that resuscitation must be started within the critical period of four minutes and therefore the time that the heart was last beating effectively must be accurately known and recorded. If the physician is present at the time of a suspected arrest his first act should be to note the time on his watch and pencil it if necessary on the bedsheet. This act should take precedence even over the calling for assistance. If he is not present at the moment of cardiac arrest, he is taking a grave responsibility if he performs a thoracotomy without having proof that the patient was alert and talking or standing up less than four minutes earlier, or if under anesthesia that he had a palpable pulse. Even within the critical time limit speed is important, for the heart that has not beaten for thirty seconds is easier to revive than the one that has been in arrest for over three minutes.

The second point to emphasize is that restarting the heart is of absolutely no avail unless oxygenation of the blood is taking place in the lungs. In other words, we are dealing with cardiorespiratory and not just cardiac resuscitation; assisted breathing has to be carried out simultaneously with cardiac stimulation. It is mechanically impossible for one physician both to massage a patient's heart and to breathe for him at the same time. He must therefore be able to count on some reasonably skilled assistance before he undertakes resuscitation. He must also be certain that the airway is not obstructed.

Given a case of sudden cardiac cessation, whether standstill or fibrillation, with the time of arrest accurately reported and with assistance summoned, the obvious thing for the physician to do first is to pound forceably on the precordium. It can do no harm and takes but a moment. At the same time any assistant on the

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[10] Stephenson, H. E., Jr., Reid, L. C. and Hinton, J. W. Some common denominators in 1200 cases of cardiac arrest. *Ann. Surg.*, 137: 731–744, 1953.

[11] Hellerstein, H. K. What is the mechanism of death? Report to Post-Graduate Seminar. University of Kansas, Feb. 26, 1957.

[12] Cole, S. L. and Corday, E. Four-minute limit for cardiac resuscitation. *J. A. M. A.*, 161: 1454–1458, 1956.

* A few cases have been reported in which complete recovery resulted after an interval of more than five minutes. A number of these are in older patients in whom the delay was measured as the time from the arrest until the heart began to contract spontaneously rather than from the arrest until the massage was commenced. Others may have been due to inaccurate estimation of the passage of time. In a few who were intubated and given assisted respiration, the artificial respiration itself may have caused some slight cerebral circulation [*13*]. It is also possible that newer technics and especially the use of hypothermia during the recovery period may render the four-minute limit obsolete. Presumably, however, the concept of the critical time limit will still apply although its duration may be extended.

[13] Thompson, S. A. The effect of mechanical artificial respiration upon maintenance of the circulation. *Surg., Gynec. & Obst.*, 84: 1059–1064, 1957.

scene should be applying artificial respiration. Two conventional airways with their external ends welded or taped together so that the combined instrument is S-shaped is satisfactory for the first few minutes, with the breather leaning over the patient's head in the usual position of the anesthesiologist. A simple airway with a rebreathing bag connected to a source of 100 per cent oxygen is more effective, and an endotracheal tube put in position by a trained anesthesiologist who can keep the lung properly expanded if thoracotomy has to be performed is the most satisfactory of all. In the absence of such facilities, mouth-to-mouth rebreathing with the tongue pulled forward and the nostrils occluded is moderately effective as a temporary measure.

Traditionally the next thing to do is to needle the heart, if possible using a long needle and advancing if necessary in more than one direction, for the mechanical stimulus to the heart muscle is probably the significant factor. Whether it is worthwhile to inject a small amount of epinephrine is questionable. Bailey found needling of the heart ineffective in his cases [*14*]. Only one of forty patients so treated revived. In the operating room it is no longer attempted. Elsewhere in the hospital it should only be considered in cases in which for one reason or another one cannot attempt cardiac massage or use an external stimulator.

The third possibility, the external electrical stimulator, has already found its place in Stokes-Adams attacks, for which it is the resuscitative method of choice. Several models have been developed and Zoll [*15*] has reported considerable success in cases proved due to cardiac standstill. Theoretically, in many respects external electric stimulation should be the salvation of the internist who rightly shudders at the thought of having to perform an emergency thoracotomy. Practically, however, there are several disadvantages. In common with pounding on the chest and needling the heart it is completely ineffective in those cases that are in ventricular fibrillation rather than standstill. It is not as certain as direct massage even in standstill and not as satisfactory because the heart is not kept under direct observation for transient arrhythmias and for estimation of the strength of spontaneous contractions. It is possible, for instance, to restore a beat that is ineffective and does not adequately circulate the blood to the vital areas. Finally, crucial time is wasted using a stimulator if thoracotomy has to be performed after all. The external electrical stimulator is therefore rarely indicated for cardiac arrest other than Stokes-Adams attacks unless cardiac massage is impracticable. For cases of ventricular fibrillation Zoll has devised an external defibrillator but his success in restoring viable patients has not been great [*16*]. There is some hazard in the use of the machine by those not thoroughly accustomed to it. Most important of all, even in the exposed heart in ventricular fibrillation, electric defibrillation is rarely possible until massage has "pinked up" the heart by driving oxygenated blood into the coronary arteries.

Finally there is open thoracotomy for cardiac massage. In the operating room this is the method of choice, and elsewhere under the proper circumstances it is certainly the most effective measure. Outside the operating room, however, the mechanics of this procedure are not easy. For the guidance of the internist who has to decide whether or not to attempt cardiac massage I have listed four questions. I believe he should run each of these rapidly through his mind before making his decision—a process that should require only a few seconds.

(1) Has the patient the fundamental health to justify restoration of life? Obviously one would not resuscitate a patient with terminal carcinoma or an overwhelming myocardial infarct. In general, this question applies more to medical than to surgical patients, for one can argue that any patient judged fit for surgery is fit for resuscitation. An illustrative exception, however, would be the patient who has been explored and then closed because of inoperable carcinoma.

(2) Can you guarantee that there is still time to institute massage (less than four minutes have elapsed)? This has already been covered but it cannot be emphasized too often.

(3) Have you the training, the equipment and the assistance necessary to undertake the procedure (both cardiac massage and assisted respiration) and to carry it through to a suc-

[14] Bailey, H. Cardiac massage for impending death under anesthesia. *Brit. M. J.*, 2: 84–85, 1941.

[15] Zoll, P. M., Linenthal, A. J., Norman, L. R., Paul, M. H. and Gibson, W. External electric stimulation of the heart in cardiac arrest. *Arch. Int. Med.*, 96: 639, 1955.

[16] Zoll, P. M., Linenthal, A. J., Gibson, W., Paul, M. H. and Norman, L. R. Termination of ventricular fibrillation in man by externally placed electric countershock. *New England J. Med.*, 254: 727, 1956.

cessful conclusion? Here the first emphasis is on the need for at least two people who are reasonably trained. The initial equipment need only be a scalpel plus one pair of hands trained to massage and a mouth and pair of lungs to do mouth-to-mouth breathing, but once massage is under way there is bleeding and eventually a skilled surgical closure in the operating room is needed. It would be tragic to restore a patient to consciousness only to have him die subsequently without anesthesia from bleeding into an open thoracotomy wound.* This last consideration makes cardiac massage impracticable, except under extraordinary circumstances, in the patient's home or in the usual doctor's office outside a hospital.

(4) Is the arrest iatrogenic? If the arrest occurs during cardiac catheterization or the injection of hemorrhoids or from an overdose of digitalis, for example, the physician feels a personal responsibility that must motivate him.

In a recent discussion of cardiorespiratory resuscitation at the Presbyterian Hospital this rather conservative approach to cardiac massage was challenged by some surgeons and anesthesiologists. Perhaps conditioned by their experience in the operating room where several patients are successfully resuscitated each year, they questioned the necessity of applying the four-minute limit too strictly. The answer I believe is to emphasize once more the great difference between cardiac massage in the operating room with surgeon, instruments and anesthesiologist all present and where cessation of the heart should be instantly appreciated (or where if there is doubt the error should be small), and outside the operating room where any or all of these may be lacking. Results bear this out when one considers the eight reported cases of successful outside-the-operating-room resuscitation in ventricular fibrillation as against the large series during major surgical procedures.

On the medical wards it is at present only the rare case of exitus that justifies cardiac massage. As training and technics improve the number may increase slightly and it may even become standard procedure to attempt resuscitation in selected instances of death associated with coronary insufficiency. It therefore behooves the internist to train himself in the simple methods for assisted respiration and to become at least familiar with the technic of cardiac massage. It is important that he be ready should the proper occasion ever arise. The four questions considered may help him make his decision more wisely and conservatively.

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* To my knowledge no case has yet been reported in which this tragedy has occurred.

Clinical Studies

Ocular Sarcoidosis*

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The earliest descriptions of sarcoidosis drew attention to the cutaneous manifestations of the disease. Nearly sixty years were to elapse before it became accepted that the eye could be involved in a similar process. Jonathan Hutchinson, who first recorded and illustrated an example of sarcoidosis of the skin [*1*], was an able ophthalmologist as well as an observant dermatologist. He was, therefore, well qualified to note any possible association between inflammatory disease of the eye and the purple plaques which he had described. His voluminous writings do not suggest that he had perceived such a link, although he does accurately record examples of subacute relapsing iridocyclitis with postcorneal precipitates, which may well have been due to sarcoidosis [*2*].

Schumaker [*3*] and Bering [*4*] first drew attention to iritis accompanying sarcoidosis. In addition to lesions of the eye, they independently noted simultaneous involvement of the parotid and submaxillary glands. In view of positive tuberculin skin reactions, they concluded that their patients had tuberculous iritis. At the same time, the Danish ophthalmologist Heerfordt [*5*] drew attention to "Febris uveoparotidea subchronica," characterised by uveitis and enlargement of the parotid glands. The condition ran a chronic and usually febrile course, was frequently complicated by cranial nerve palsies, especially of the seventh cranial nerve, and was associated with pleocytosis of the cerebrospinal fluid. Heerfordt described three cases and referred to others in the literature. Since the latter had been ascribed to mumps, Heerfordt believed that his examples were due to the same cause.

During the following quarter century the aetiology of Heerfordt's syndrome was fiercely debated. Two main schools of thought favoured either mumps or tuberculosis. Garland and Thomson [*6*] favoured a tuberculous aetiology on the basis of their observations of one case and a review of forty-six examples from the literature. They recommended that the syndrome be termed "uveo-parotid tuberculosis."

Controversy ended when Bruins Slot [*7,8*], Longcope and Pierson [*9*] and Pautrier [*10,11*] identified uveoparotid fever as but another manifestation of sarcoidosis. Pautrier particularly contended that it was unrelated to tuberculosis. Any structure of the eye may be involved by sarcoid tissue. The various lesions are comprehensively surveyed by Levitt [*12*] and more recently in Longcope and Freiman's [*13*] study of sarcoidosis.

The suggestion that erythema nodosum with bilateral hilar lymphadenopathy may be a manifestation of sarcoidosis is of recent standing [*14,15*]. This syndrome may be associated with ocular sarcoidosis [*16,17*].

MATERIAL AND METHODS

The 200 patients, who have been personally studied, showed clinical or radiological features of sarcoidosis supported by histological evidence of sarcoid tissue. Patients with clinical, radiological and immunological features of sarcoidosis have been excluded if there was no histological confirmation. The series includes fifty patients (25 per cent) with ophthalmic involvement.

Clinical and ophthalmoscopic examination has been augmented by radiographs of chest, hands and feet. Mantoux tests have been routine, and Kveim tests [*18,19*] were performed in 149 cases. Paper zone electrophoresis of the plasma proteins and estimation of the serum albumin and globulin levels by the biuret method were undertaken in 148 patients. Serum globulin levels above 3.5 gm. per 100 ml. or an electrophoretic pattern showing relative preponderance of α_2, β or γ globulin were considered abnormal.

Histological evidence of sarcoid tissue has been obtained from various sources by biopsy and at necropsy. The Hayes-Martin drill has been used for skin biopsy.

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TABLE I
PRESENTING FEATURES OF OCULAR LESIONS

Type of Ocular Lesion	Patients (no.)
Iridocyclitis	30
Subacute (11)	..
Chronic (19)	..
Conjunctivitis	8
Phlyctenular (4)	..
Non-specific (4)	..
Keratoconjunctivitis	7
Conjunctival follicles	3
Periphlebitis retinae	1
Cataract	1
Total	50

OCULAR LESIONS

Fifty (25 per cent) of the 200 patients suffered from various ocular manifestations of sarcoidosis. The most common mode of presentation was subacute or chronic iridocyclitis, and this was followed in frequency by some form of conjunctival involvement. (Table I.)

Subacute Iridocyclitis. This was noted in eleven patients; it was bilateral in seven, left-sided in three and involved the right eye alone in one patient. The onset was always sudden with pain and mistiness of vision. The affected eyes showed ciliary congestion, turbidity of the aqueous humour and occasional fine keratic precipitates circulating in the anterior chamber. One patient was found to have three white choroidal nodules adjacent to the superior temporal branch of the retinal artery.

Evidence of involvement of other tissue systems was widespread. (Table II.) Lymphadenopathy was noted in seven and splenomegaly in two patients. Erythema nodosum or other transient skin lesions occurred in four patients. In two patients transient facial palsy developed, one of which was associated with transient subacute meningitis and the other with parotid and submaxillary enlargement. The latter exemplified the syndrome originally defined by Heerfordt [*5*].

Apart from these clinical associations, other features, when sought, also suggested the diagnosis of sarcoidosis. There were significant abnormalities in the chest radiographs in ten, the Mantoux test was negative in seven, and the Kveim test was positive in ten patients.

Chronic Iridocyclitis. Nineteen patients, predominantly female, had shown uveal tract abnormalities for longer than one year. In all but one, the changes were bilateral. The onset was insidious with some pain and blurring of vision in the majority; three patients had no ocular symptoms and the signs were revealed only by ophthalmoscopic examination. Ciliary congestion, implying ocular inflammation, was absent. Instead, there were numerous grey precipitates and cellular particles were seen circulating in the anterior chamber. These grey fat-like nodules on the posterior corneal surface have been aptly described "mutton-fat" keratic precipitates. In addition, other features emphasising the chronicity of the process included posterior adhesions of iris to lens, iris nodules, lens opacities or cataracts, corneal degeneration and secondary glaucomatous changes. In two patients the left eye was excised for secondary glaucoma, following obstruction of

TABLE II
INVOLVEMENT OF OTHER TISSUES IN OCULAR SARCOIDOSIS

Type of Ocular Lesion	Patients (no.)	Other Tissues Involved						
		Lungs	Skin	Lymph Nodes	Spleen	Bone	Lacrimal Glands	Salivary Glands
Subacute iridocyclitis	11	10	4	7	2	0	0	2
Chronic iridocyclitis	19	16	8	7	4	5	1	1
Conjunctivitis	8	7	5	2	2	0	0	0
Keratoconjunctivitis	7	4	4	4	0	0	3	3
Conjunctival follicles	3	2	2	3	1	1	0	1
Periphlebitis retinae	1	1	1	1	0	0	0	0
Cataracts	1	1	0	1	1	0	0	0

the angle of the anterior chamber by exudates. Sarcoid lesions were demonstrable in the ciliary body, choroid and retina of the excised eyes, underlining the fact that the disease is liable to involve the posterior as well as the anterior uveal tract. Patchy choroiditis, choroidal tubercles and retinal oedema were each seen in different patients in this group, but anterior uveitis often renders it difficult to visualise the posterior uveal tract. Posterior uveitis is undoubtedly more common than is realised.

Accompanying clinical manifestations of sarcoidosis were also long-standing. Skin lesions occurred in eight patients and were associated with bone cysts in five. (Table II.) Lymphadenopathy persisted in seven and splenomegaly in four patients. Enlargement of lacrimal or submaxillary glands, palatal involvement and transient Bell's palsy were each noted once. Tonsillar involvement was noted in two patients.

Intrathoracic involvement in sixteen patients was revealed by predominantly long-standing changes. In only four of these patients has radiographic clearing been seen; in the remainder, over a varying number of years, irreversible pulmonary fibrosis has developed.

The Mantoux test was negative, at a strength of 100 tuberculin units, in sixteen of the nineteen patients, and the Kveim test was positive in nine of the eleven patients in whom it was performed.

Conjunctivitis. In this group of eight patients, phlyctenular or non-specific conjunctivitis appeared at the same time as other manifestations of sarcoidosis. Since it was a troublesome affliction, early medical advice was sought.

Phlyctenular conjunctivitis in four young adult women was left-sided in three and bilateral in one. In each instance it coincided with the onset of erythema nodosum and was accompanied by bilateral hilar lymphadenopathy.

Tuberculin skin tests to a strength of 100 tuberculin units were negative in two and only weakly positive in the other two. Kveim tests were positive in three patients. In each case, the episode subsided without recurrence within three weeks.

Bilateral non-specific conjunctivitis occurred in three men and in one woman. There was concurrent involvement of the lungs in three, and the skin, lymph nodes or liver in each patient. The Mantoux test was positive in two and the Kveim test in three of the four patients. Conjunctivitis subsided without recurrence within two weeks.

Keratoconjunctivitis occurred in five females and two men. Dry eyes due to keratoconjunctivitis sicca proved a distressing symptom in four patients (three patients with and one without obvious lacrimal gland involvement). Corneal ulceration was a complicating factor in one instance. Fortunately, keratoconjunctivitis sicca did not prove to be persistent, for it resolved spontaneously after six months in one and was relieved by oral and topical cortisone in the other three patients. The remaining three patients, without dry eyes, showed corneal staining and degenerative changes. This did not provoke troublesome symptoms, and signs were only noted on routine ophthalmoscopic examination.

Intrathoracic, cutaneous and lymph node involvement were noted in four and the lacrimal and salivary glands were enlarged in three patients. The Mantoux test was negative in five of the seven patients and the Kveim test positive in all five in whom it was performed.

Conjunctival Follicles. Three patients exhibited nodular collections in the conjunctival fold of the lower eyelid. The patients were aware of their presence, but troublesome symptoms did not occur. All three patients had generalised lymphadenopathy, two showed persistent intrathoracic and skin changes, and one also had parotid and bone involvement. These follicular collections gradually became less evident in the course of a year in one patient, and the lesions disappeared under the influence of local and systemic corticosteroid therapy in the other two patients. The Mantoux test was negative in two patients and the Kveim test was negative in the only patient in whom it was performed.

Periphlebitis Retinae. One patient with lupus pernio, pulmonary mottling and generalised lymphadenopathy was found to have periphlebitis retinae, retinal haemorrhages and retinitis proliferans of the left eye. This was associated with but insignificant ocular symptoms, possibly because the patient was too distracted by the associated disfiguring skin lesions. The Mantoux test was negative and the Kveim test was not performed. The ocular condition has persisted with little change for five years.

Cataracts. Cataract formation was observed as an end-result of chronic iridocyclitis. In one fifty-five year old woman, however, bilateral cataracts were the earliest presenting features, together with lymphadenopathy, splenomegaly and extensive pulmonary mottling. The Man-

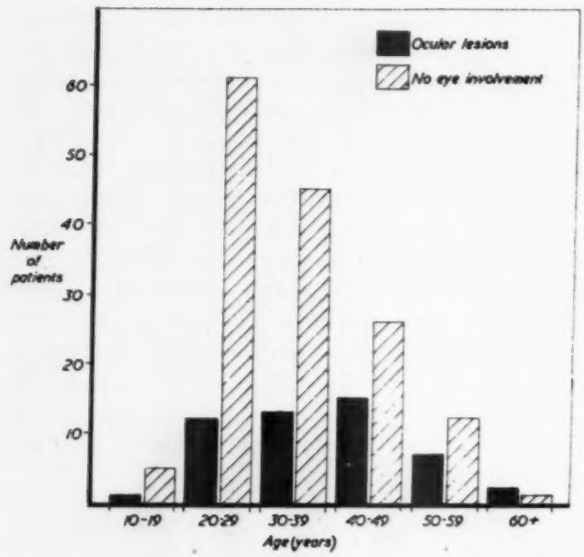


FIG. 1. The age at apparent onset of sarcoidosis in fifty patients with ocular lesions compared with 150 patients without eye involvement.

toux test was negative and so was the Kveim test at this late stage of the disease.

RELATIONSHIP OF OCULAR TO GENERALISED INVOLVEMENT

Age and Sex Incidence. The peak age incidence at the onset of ocular symptoms lies in the forty to fifty decade with a mean age at onset of thirty-nine years. (Fig. 1, Table III.) The range is similar to that observed for skin lesions, in which the peak occurs in the forty to fifty decade with a mean age at onset of forty-two years [*20*]. By comparison, the age at onset of 150 patients without ocular disease has a peak incidence in the twenty to thirty decade and a mean age of thirty-two years.

TABLE III
AGE AND SEX DISTRIBUTION

Group	Patients (no.)	Age at Onset (yr.)		Females	
		Range	Mean	No.	%
Ocular group	50	18–66	39	35	70
Non-eye group	150	13–63	32	79	53
Total	200	13–66	35	114	57

Patients with subacute iridocyclitis had an average age at onset of thirty-four years compared with forty years for the group with chronic iridocyclitis.

Sarcoidosis affects both sexes to about the same extent but in those patients with ocular lesions (and again like those with skin lesions) there was a conspicuous preponderance of females. (Table III.)

Intrathoracic Involvement. This occurred in forty-one of fifty patients (82 per cent) with ocular disease. The changes ranged from bilateral hilar lymphadenopathy to diffuse pulmonary mottling without hilar gland enlargement. (Table IV.) Those with long-standing ocular disease had intrathoracic changes at an

TABLE IV
INTRATHORACIC RADIOLOGICAL CHANGES

Type of Ocular Lesion	Patients (no.)	Clear Chest Roentgenogram	Bilateral Hilar Lymphadenopathy	Hilar Lymphadenopathy plus Pulmonary Mottling	Diffuse Pulmonary Mottling	Subsequent Complete Clearing	
						No.	%
Subacute iridocyclitis	11	1	9	1	..	10	100
Chronic iridocyclitis	19	3	3	3	10	4	25
Conjunctivitis	8	1	5	..	2	6	75
Keratoconjunctivitis	7	3	1	2	1	2	29
Conjunctival follicles	3	1	1	..	1	0	...
Periphlebitis retinae	1	..	..	..	1	1	...
Cataract	1	..	..	1	..	0	...
Total	50	9	19	7	15	23	56

TABLE V

INVOLVEMENT OF OTHER TISSUES IN SARCOIDOSIS WITH AND WITHOUT OCULAR INVOLVEMENT

Group	Patients (no.)	Other Tissues Involved													
		Lungs		Skin		Lymph Nodes		Spleen		Bone		Lacrimal Glands		Salivary Glands	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Ocular	50	41	82	24	48	25	50	10	20	6	12	4	8	7	14
Non-ocular	150	141	94	71	47	50	33	17	11	5	3	2	1	1	1
Total	200	182	91	95	47	5	37	27	13	11	5	6	3	8	4

older stage of development than those with transient lesions. This was also reflected in the incidence of radiological clearing, which occurred in the majority of those with subacute iridocyclitis and conjunctivitis but only in the minority of those with chronic iridocyclitis and keratoconjunctivitis.

Complete radiological clearing has occurred in one-half of the patients with ocular lesions.

Skin Lesions. These included lupus pernio, maculopapular eruptions, persistent plaques, scars or erythema nodosum [*20*]. They occurred in one-half of the series; the incidence was the same in the groups with and without ocular disease. (Table v.) The simultaneous occurrence of skin plaques or erythema nodosum with granulomatous uveitis should always arouse the suspicion of sarcoidosis.

Lymphadenopathy. Enlarged palpable lymph nodes were present at some stage of the disease in 50 per cent of patients with ocular disease, compared with 33 per cent of the group without eye manifestations or 37 per cent for the whole series. (Table v.)

Splenomegaly. A spleen was palpable in one-fifth of patients with ocular sarcoidosis, being somewhat more frequent than in those without ocular disease. (Table v.)

Bone Cysts. Cystic changes in bones of the hands or feet were found radiologically in six patients, five of whom had chronic iridocyclitis and one with conjunctival follicles. (Table II.) All had accompanying skin lesions, so the detection of bone changes did not provide diagnostic information not already afforded by examination of the skin.

Lacrimal and Salivary Gland Enlargement. Enlarged lacrimal glands were observed in four patients, three of whom had associated keratoconjunctivitis sicca and the other chronic iridocyclitis. Salivary gland enlargement, principally parotid, occurred in seven patients. (Tables II and v.) Two patients had the combination of lacrimal and parotid gland enlargement with dry eyes resembling Sjögren's syndrome.

Serum Globulin Levels. Raised or abnormal serum globulin levels occurred in forty of 148 patients (27 per cent) in whom they were determined. There was no significant difference as to whether ocular lesions were present or absent.

SKIN TESTS

Mantoux Reaction. Thirty-six patients (72 per cent) with ocular involvement gave negative results with 100 tuberculin units, compared with 56 per cent in the non-ocular group (Table VI) or 60 per cent of the whole series. Positive reactors almost always gave negative results at higher dilutions, and 100 tuberculin units were necessary to elicit a positive response.

Kveim Tests (*Table* VII). These tests provided histological evidence of sarcoid tissue in 129 of 149 patients. They were positive in thirty of thirty-six patients (83 per cent) with ocular sarcoidosis.

HISTOLOGY

Histological examination revealed well defined follicles composed of large pink-staining epithelioid cells, occasional giant cells, a thin peripheral ring of lymphocytes and inconspicu-

TABLE VI
RESULTS OF MANTOUX TESTS

Type of Ocular Lesion	Patients (no.)	Mantoux Tests (100 tuberculin units)	
		Positive	Negative
Subacute iridocy litis...	11	4	7
Chronic iridocyclitis...	19	3	16
Conjunctivitis.....	8	4	4
Keratoconjunctivitis...	7	2	5
Conjunctival follicles...	3	1	2
Periphlebitis retinae...	1	0	1
Cataracts.....	1	0	1
Total			
Ocular group.....	50	14(28%)	36(72%)
Non-ocular group...	150	66(44%)	84(56%)

TABLE VII
RESULTS OF KVEIM TESTS

Group	Patients (no.)	Kveim Test (0.2 ml.)			
		Positive		Negative	
		No.	%	No.	%
Ocular.....	36	30	83	6	17
Non-ocular....	113	99	87	14	13
Total.....	149	129	86	20	14

ous central necrosis. The absence of caseation and of acid-fast bacilli and the preservation of the reticulin network served to distinguish it from tuberculous tissue.

Apart from the results of the Kveim test, histological evidence of sarcoid tissue was also found in various tissues by biopsy in thirty-seven patients and at necropsy in one. Histological confirmation of sarcoid tissue in the ocular series was obtained from skin (twelve patients), lymph node (8), liver (7), enucleated eye (2), tonsil (2), and once from nasal mucosa, parotid gland, lacrimal gland, palate, bone and breast.

Blind conjunctival biopsies were performed in ten patients but in no instance did they reveal sarcoid tissue at a time when this was obtained from other tissues.

TREATMENT

Within a few weeks of the onset of symptoms eight of the eleven patients with subacute iridocyclitis had received intensive corticosteroid therapy. Six received local cortisone eye drops, and in two these were preceded by subconjunctival injections of hydrocortisone. Four patients received oral cortisone or prednisolone. In all instances, there was rapid relief of symptoms and subsidence of the signs of ocular inflammation without recurrence within six months. All other clinical and radiological features of sarcoidosis had also cleared within one year, irrespective of whether or not cortisone administration had been systemic.

In the group of patients with chronic iridocyclitis, corticosteroid therapy had been delayed for one to fourteen years, with an average of five years. In the majority, iridocyclitis had developed several years before the advent of cortisone, and they had been subjected to various regimens in vogue at that time. These included complete dental extractions, maxillary antrum lavage, tonsillectomy, cholecystectomy, autogenous vaccines, provocative tuberculin and typhoid vaccine injections, cyclodiathermy and antituberculous chemotherapy. These regimens were later followed by excision of the eye and enucleation of cataracts in two patients each and by iridectomy in another. Eventually, cortisone became available and was given locally or orally to fourteen patients. Slight benefit was sometimes observed but the results of treatment were understandably disappointing at this late stage of irreversible ocular fibrosis.

Conjunctivitis, whether phlyctenular or nonspecific, subsided without special treatment within three weeks.

Combined oral and topical cortisone provided early and rapid relief of symptoms in three patients with keratoconjunctivitis sicca and resolved conjunctival follicles in another two patients.

There was no effective therapy for the patient with periphlebitis retinae and the patient who presented at the late stage of cataract formation.

COMMENTS

From a survey of the literature, Longcope and Freiman [*13*] found ocular disease in 177 of 651 cases (27 per cent) of sarcoidosis; this agrees closely with the incidence of 25 per cent in the present series.

The most common affliction is a granulom-

atous uveitis, which may be subacute or chronic. The differences in the onset, symptoms and signs, and in the natural history of these two stages is striking. (Table VIII.) Subacute iridocyclitis had a sudden onset, clinical evidence of inflammation, and eventual complete clearing within six months, whereas chronic iridocyclitis developed insidiously and persisted because of complicating ocular fibrosis. Subacute iridocyclitis was accompanied by transient skin lesions, notably erythema nodosum, and transient intrathoracic changes, principally bilateral hilar lymphadenopathy. Bone cysts were not a feature of this phase. In contrast, chronic iridocyclitis has been accompanied by indolent skin lesions; persistent intrathoracic changes and bone changes have been common. The chronicity of the process in one system is a good index of chronicity in others, whether it be eyes, lungs, skin or bones.

In seeking a possible explanation for these differences, one predominating factor is the introduction and use of the cortisone group of drugs. The majority of patients with subacute iridocyclitis were treated with these drugs within days or at the most weeks of the onset of symptoms, whereas those with chronic iridocyclitis had waited several years for the introduction of corticosteroid therapy. Indeed, they had been subjected to various passing fashions, including the hunt for and eradication of focal sepsis. By the time cortisone became available, irreversible ocular fibrosis had developed and made any permanent benefit unlikely.

There can be little doubt that patients who are diagnosed and treated early have a favourable outcome and are left with no residual ocular disability, whereas those who remain undetected and untreated are liable to become blind. The group with chronic iridocyclitis illustrate well the protracted course and high incidence of complications not observed in the group receiving early cortisone therapy. Such therapy has almost certainly changed the natural history of sarcoid iridocyclitis.

This cannot be the complete answer, for three patients with subacute iridocyclitis received no corticosteroids and yet recovered. However, the eye changes had developed with erythema nodosum and bilateral hilar lymphadenopathy, a syndrome well recognised to be transient [*17*]. Furthermore, another four patients with subacute iridocyclitis had only received the benefits of topical ophthalmic

TABLE VIII
IRIDOCYCLITIS IN THIRTY PATIENTS

Data	Subacute	Chronic
No.	11	19
Age at onset	34	40
Onset	Sudden	Insidious
Ciliary congestion	Present	Absent
Signs	Turbidity of aqueous humour K.P.* in anterior chamber	Grey fatty nodules in posterior corneal surface
	Choroiditis Retinal oedema	
Sequelae	Nil	Lens opacities Synechiae: iris → lens Glaucoma Cataracts Blindness
Duration before cortisone	Nil	1–14 years (average 5)
Lungs	10	16
X-ray clearing	10 (100%)	4 (25%)
Skin lesions	Transient	Persistent
Bone cysts	0	5

* Keratic precipitates.

cortisone, but during the ensuing year hilar adenopathy had also regressed. The favourable outcome of subacute compared with chronic iridocyclitis can therefore be related to spontaneous remission and early recognition as well as to corticosteroid therapy.

Keratoconjunctivitis sicca may likewise prove a distressing feature of sarcoidosis. In two instances simultaneous salivary gland involvement, causing dry mouth, superficially resembled Sjögren's disease, particularly since diffuse pulmonary mottling may be evident in both diseases. Nevertheless, the patients in this group demonstrated normal mucosal secretions elsewhere, they did not have arthritis, and definitive histological proof of sarcoidosis was obtained. One patient with keratoconjunctivitis sicca showed spontaneous resolution after six months, and in the other three corticosteroid therapy was followed by an earlier and more rapid relief of symptoms.

The importance of early diagnosis in sarcoidosis has been stressed [*21*]. With ocular disease this becomes of paramount importance if distressing sequelae are to be avoided. Granulomatous uveitis, keratoconjunctivitis sicca and

conjunctival follicles should always arouse the suspicion of sarcoidosis, and other clinical and radiological evidence of the disease should be sought. The relationship of ocular to generalised involvement has been emphasised, the most frequent associations being intrathoracic changes, skin lesions and lymphadenopathy. (Table v.)

The clinical diagnosis should be confirmed, whenever possible, by histological proof. In the present ocular series it was obtained from various accessible tissues including aspiration liver biopsy and also by means of the Kveim test. Blind conjunctival biopsy has been recommended [*22*] but it is difficult to distinguish sarcoid tissue from a foreign body giant cell reaction in the tiny fragment submitted. This technic was of no help in the present series.

The natural course of sarcoidosis is towards spontaneous healing by fibrosis. In the eye this may cause serious complications, so ocular involvement is an absolute and prime indication for the treatment of sarcoidosis by early and energetic corticosteroid therapy. It should always be administered topically, and it should also be considered orally for all but the most superficial and transient ocular lesions. Recently, oral triamcinolone has proved to be effective and may be considered an alternative to prednisone and prednisolone.

SUMMARY

1. Ocular lesions were observed in fifty of 200 patients with sarcoidosis. They included subacute or chronic iridocyclitis, conjunctivitis, keratoconjunctivitis sicca and conjunctival follicles. The differences between subacute and chronic iridocyclitis are striking. This is in part due to corticosteroid therapy, which has probably changed the natural history of sarcoid iridocyclitis.

2. Involvement of other tissues is correlated with ocular disease and the pattern is compared with that observed in patients without eye involvement. Ocular sarcoidosis is commonly accompanied by intrathoracic and cutaneous lesions and by lymphadenopathy. Reduced secretions due to simultaneous lacrimal and salivary gland involvement may superficially resemble Sjögren's syndrome.

3. Compared with those without eye lesions, patients with ocular sarcoidosis belonged to an older age group, females predominated and Mantoux tests were more often negative.

4. The clinical diagnosis should be confirmed, whenever possible, by histological evidence of sarcoid tissue. This was obtained by biopsy of various tissues and also by means of the Kveim test, which was positive in the majority of patients with ocular disease. Blind conjunctival biopsy was of no diagnostic help.

5. The natural course of sarcoidosis is towards spontaneous healing by fibrosis. In the eye this may cause serious complications, so ocular involvement is an absolute indication for early and energetic corticosteroid therapy.

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Bronchopulmonary Sarcoidosis*

Some Unusual Manifestations and the Serious Complications Thereof

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IT has been emphasized by some (and disputed by others) that one of the hallmarks of generalized sarcoidosis is its rather benign course [*1*], in the face of rather massive organ involvement and replacement by granulomatous lesions. It is a well known fact that patients with this disease often present themselves with trifling complaints or even with symptoms completely unrelated to it, and upon further investigation show extensive involvement of the lymphatics, liver, spleen or lungs of which the patient is completely unaware. In no area of medicine is this more true than in the field of chest disease in which sarcoidosis so frequently comes under suspicion because of the findings on a routine chest roentgenograms. The discovery of bilateral hilar adenopathy and/or diffuse miliary or nodular infiltrates, linear or reticular striations, localized infiltrates, is suggestive of the diagnosis [*2–7*]; and when the patient is a Negro with a paucity of symptoms and a negative tuberculin skin test, sarcoidosis is the disease to be strongly considered.

At a large city hospital with a predominently Negro patient population, we have had opportunity to deal with many unusual aspects of sarcoidosis. In many of the cases to be described the afflicted patients presented themselves with serious complications of their underlying disease.

Because of the occasional incidence of a chronic indolent form of lymphohematogenous tuberculosis, which on pathologic examination of a small specimen of biopsy material revealed non-caseating granuloma, the pathologist was often unwilling or unable to distinguish between the non-caseating form of tuberculosis or other similar granulomatous diseases, and the granulomas of sarcoidosis. Difficulty also arose in identifying biopsy material of sarcoidosis, particularly during its proliferative stage, when oversized zones of focal necrosis in the granulomas were encountered. It would appear that the more experience pathologists gain in encountering the borderline degrees of caseation in tuberculosis and focal necrosis in sarcoidosis, the less willing they become to identify small biopsy samples of various organs as definite tuberculosis or sarcoidosis. (It should be mentioned that the Ziehl-Neelsen and the periodic acid-Schiff stain for fungi were also employed in the study of our biopsy material in all the cases to be described.) But despite the difficulties encountered at times in the use of biopsies from multiple sites we have come to rely increasingly on the pathologist to give us an indication as to the kind and extent of involvement with sarcoidosis.

We have had a limited albeit disappointing experience with the Nickerson-Kveim skin test because of the difficulty in securing reliable standardized testing suspension [*8,9*], the nature of our patient population with frequent poor follow-up and lack of opportunity for biopsy of the skin test site, and a relatively high incidence of false negative tests. The greater ease and reliability of obtaining biopsy material from the organs or nodes involved, under these circumstances has led us to depend largely upon biopsies for confirmation of the diagnosis.

Some of the unusual manifestations and complications of bronchopulmonary sarcoidosis will be described in the following sections.

Sarcoidosis Simulating Metastatic Lung Disease. It is not sufficiently appreciated that sarcoidosis may appear on routine chest films in the form of diffuse large parenchymal nodules

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FIG. 1. Case 1. Roentgenogram of the chest showing large bilaterally symmetrical nodular densities associated with hilar adenopathy.



FIG. 2. Same case. Marked regression of the parenchymal nodules approximately three weeks after the institution of prednisone therapy. The hilar adenopathy is unchanged.

resembling the "cannon ball" metastases so often originating from a renal cell carcinoma or metastatic sarcoma. According to Kerley [*10*] the nodules are due to involvement by sarcoid granuloma of lymphoid foci in the lung parenchyma.

The nodular densities seen in sarcoidosis of the lung are usually small, 1 to 5 mm. in Garland's series [*2*], and 3 mm. in Kerley's series [*10*], but they may also achieve large size, 10 to 30 mm. as in McCord and Hyman's two cases [*11*], which were the first case reports of pulmonary sarcoidosis imitating diffuse metastatic lung disease of the "cannonball type."

CASE 1. H. B., a twenty-one year old Negro male stock clerk, was admitted to D. C. General Hospital on July 8, 1957 with complaints of easy fatiguability of six months' duration and a fourteen pound weight loss. Two months prior to admission he had been rejected for military service because of findings on a chest roentgenogram and had been referred to our hospital. For one month before admission he had had a non-productive cough. The past medical history was not otherwise contributory. The patient had been born and raised in the District of Columbia. There was no history of exposure to tuberculosis.

Physical examination revealed a slender Negro man weighing 128 pounds, with blood pressure 95/60 mm. Hg, pulse 86, temperature 100°F. The positive physical findings included palpable small firm non-tender lymph nodes involving the cervical, submandibular, axillary and inguinal areas. The skin showed small flat brownish areas of pigmentation over the back and extremities. The liver was palpable 4 cm. beneath the costal margin.

Laboratory work revealed a white blood cell count of 3,400 per cu. mm. with 42 neutrophils, 45 lymphocytes, 5 monocytes and 8 eosinophils. The hematocrit was 49 per cent. The urinalysis was within normal limits. Serological tests were negative. The thymol turbidity test was 2.3 units; serum alkaline phosphatase 3.7 units, total protein 7.3 gm. per cent with an albumin of 4.2 gm. and globulin 3.1 gm.; bromsulphalein 10 per cent dye retention; and serum calcium 9 mg. per cent. The prothrombin was within normal limits. The PPD, histoplasmin and coccidioidin skin tests were negative.

Serial chest films (Fig. 1) revealed several large nodular opacities up to 30 mm. in size scattered throughout both lung fields, with bilateral hilar adenopathy. Metastatic lung disease was suggested by the "snow ball"-like appearance of the nodular lesions, as seen with renal cell carcinoma or sarcoma. An intravenous pyelogram was negative.

On July 17, 1957, a left scalene node biopsy for sarcoidosis was performed, revealing non-caseating granuloma. Ziehl-Neelsen and periodic acid-Schiff stains for fungi were negative. A gastrocnemius muscle biopsy was negative for granuloma but a liver biopsy showed diffuse non-caseating granuloma.

The patient's course in the hospital was characterized by fever up to 102.8°F. and a 3 pound weight loss. The patient was otherwise asymptomatic except for one episode of pleuritic pain in the right side of his

chest. On August 8, 1957, following receipt of the pathological report, administration of prednisone, 30 mg. per day, was instituted. On this regimen there was regression of the nodular chest lesions evident on x-ray films. (Fig. 2.) The patient was discharged to follow-up by the chest clinic on August 14, 1957.

Comment: In this patient the association of bilateral symmetrical hilar adenopathy [*12*] with the large nodular parenchymal densities was the main radiologic feature suggesting sarcoidosis. Because of the unusual size of the parenchymal nodular lesions, which are not commonly so large in sarcoidosis, the alternative possibility of metastatic lung disease was first considered. Recently another example of a relatively benign process producing this appearance on roentgenograms was described as a manifestation of chicken pox pneumonia [*13*]. We have also seen acute histoplasmosis involving the lung produce such large nodular opacities, with later regression to diffuse parenchymal calcifications.

Middle Lobe Syndrome. The causes of compression of the middle lobe bronchus, with distal atelectasis, pneumonitis and bronchiectasis, are many. The reason for this susceptibility to compression is apparently related to the small lumen of the middle lobe bronchus and its emergence at an almost right angle from the intermediate bronchus. The group of lymph nodes surrounding the middle lobe bronchus at its origin drain not only the middle lobe but also the lower right lobe and thus are subject to enlargement in the presence of inflammatory processes in either lobe. Among the causes of the middle-lobe syndrome previously reported are tuberculosis, carcinoma, hilar adenopathy related to inflammatory reaction secondary to lower esophageal trauma, lipoid pneumonia, histoplasmosis and a few previously reported cases of sarcoidosis [*14–16*].

It is a curious fact that despite frequent massive involvement of mediastinal nodes in sarcoidosis, actual bronchial compression with stenosis, inadequate drainage and all its sequellae is comparatively uncommon. The reasons for this are probably lack of perinodal inflammatory reaction with subsequent distortion of the parenchymal architecture, inadequate drainage, inflammation and still further enlargement of nodes in the drainage pathway, resulting in a vicious cycle insofar as middle lobe bronchial compression is concerned.

The following case is an instance of sarcoidosis involving the middle lobe peribronchial nodes causing pneumonitis and "drowning" of the lobe, due to retained secretions as manifested by bulging upward of the short fissure as seen in the right lateral chest view.

Case II. L. S. (Hospital No. E-14399), a forty-two year old Negro male chronic alcoholic, was admitted to D. C. General Hospital for the third time on October 15, 1953 because of a two-week illness characterized by fever, cough, chills, shortness of breath and a one-day history of sharp pain in the right lower anterior chest accentuated by deep inspiration. A chest roentgenogram taken at the Health Department four months prior to admission was reportedly negative. His previous admissions had been in July 1952 for treatment of delirium tremens and again in November 1952 for blood loss secondary to severe epistaxis requiring a transfusion of one unit of blood.

Physical examination on admission revealed an acutely ill Negro man with marked respiratory distress, blood pressure 120/68 mm. Hg, pulse 92, temperature 104°F., respiration 34. Positive findings in addition to fever and tachypnea were dehydration, carious teeth, and rales, decreased breath sounds, dullness to percussion and increase in tactile fremitus of the right lower anterior chest. The liver was palpable 5 cm. beneath the costal margin.

Chest roentgenograms (Figs. 3 and 4) showed consolidation of the middle lobe. The white blood cell count was 11,000 per cu. mm. with 80 per cent neutrophils, 13 per cent lymphocytes, 6 per cent monocytes, 1 per cent eosinophils. The hematocrit was 29 per cent, the hemoglobin 10 gm. per cent and the icterus index 25. Urinalysis was within normal limits. The blood urea nitrogen was 50 mg. per cent, total protein 7.8 gm. per cent with 4 gm. albumin and 3.8 gm. globulin. The cephalin flocculation test was 4-plus and the thymol turbidity test was 10 units. Results of tuberculin tests were negative. An electrocardiogram showed complete right bundle branch block.

The course in the hospital was marked by prolonged fever and anemia, with slow response to administration of tetracycline subjectively but without clearing of the chest roentgenogram. On November 7, 1953, bronchoscopy was performed because of the slow subjective improvement and continued middle lobe consolidation. It was noted by the bronchoscopist that the orifice of the middle lobe bronchus was edematous and blocked with yellowish secretions. Multiple sputums were negative for acid-fast bacilli, and positive for alpha streptococci, diptheroids and staphylococci on two occasions.

Because of continued lack of clearing on adequate treatment with penicillin, broad-spectrum antibiotics, nebulization, potassium iodide and postural drainage, it was decided that surgery was the next



FIG. 3. Case II. Consolidation of the middle lobe caused by obstruction of the middle lobe bronchus by lymph nodes due to sarcoidosis.



FIG. 4. Same case. Lateral view demonstrates bulging of short fissure indicative of obstruction with distal infection.

step. Under general anesthesia, middle lobe lobectomy was performed. The lobe was found to be completely atelectatic. Surrounding and compressing the origin of the middle lobe bronchus were several enlarged lymph nodes. Microscopic section of the enlarged lymph nodes compressing the bronchus revealed diffuse non-caseating granuloma with giant cells showing Schaumann bodies and crystals. Sections of the lung parenchyma revealed loss of aeration with multiple non-caseating granuloma. The patient had an uneventful postoperative course.

Comment: This case serves to illustrate the fact that middle lobe atelectasis and chronic pneumonitis may arise from a wide variety of etiologic factors [*17*], the nature of which can be disclosed only by surgical exploration and pathologic study of the resected specimen. The finding of right bundle branch block suggested the possibility of sarcoidosis of the heart. Such significant electrocardiographic abnormalities may be the only indication of myocardial involvement by sarcoid granulomas.

Honeycomb Lungs Due to Diffuse Sarcoidosis of the Lung Parenchyma with Recurrent Spontaneous Tension Pneumothorax. Diffuse cystic changes, or so-called honeycomb lungs, secondary to parenchymal infiltration has been described in a few unusual entities involving the lung. Among them are Hand-Schüller-Christian disease [*18*], tuberous sclerosis [*19*], muscular cirrhosis of the lungs [*20*] and scleroderma. The pathologic changes which occur in these cases include transformation of the alveoli and bronchioles into small cystic dilatations, and thickening of the interstitial septums. The cysts have a tendency to enlarge gradually as time goes on and eventually to rupture, producing spontaneous pneumothorax, frequently of the tension variety with shift of the mediastinal structures into the opposite hemithorax. Since the chest x-ray film presents a somewhat nodular appearance, and often, at least early in the course, cystic areas are not obvious, the usual working diagnosis is often miliary tuberculosis.

We have had occasion to see a case recently which presented this honeycomb cystic appearance and in which recurrent pneumothorax was a problem. On pathologic study, sarcoidosis was found to be the etiologic factor.

CASE III. M. H. (Hospital No. 44065), a twenty-eight year old Negro woman was admitted to D. C. General Hospital for the second time on April 7, 1957 because of extreme shortness of breath. The onset of her illness went back eight years at which time she had had a chest roentgenogram taken because of weight loss. She had been told that she had pulmonary tuberculosis and had been "followed for one year." No report on this film was available.

Her first admission to the D. C. General Hospital had been from February 10, 1955 to February 20,



FIG. 5. Case III. Diffuse nodular densities in both lungs with small cystic lesions most marked in the upper right lobe.



FIG. 6. Same case. Intercostal tube drainage for left spontaneous pneumothorax. The mediastinal structures are displaced to the right.

1955, because of a one-week illness characterized by cough, increasing shortness of breath, stuffy nose and pain in the left side of the chest. Physical examination on admission had revealed a febrile dehydrated Negro woman with injected pharynx and decreased breath sounds in both lower lung fields and coarse rales in the lower right lobe. Laboratory work demonstrated a white blood cell count of 4,700 per cu. mm. with 77 per cent neutrophils, 4 per cent bands, 13 per cent monocytes and 6 per cent lymphocytes. The blood urea nitrogen was 7 mg. per cent, fasting blood sugar 80 mg. per cent, serological test was negative, urinalysis was within normal limits. A sputum culture showed diphtheroids and was negative for acid-fast bacilli by smear and culture on four occasions. Blood cultures were negative on three occasions. A chest roentgenogram (Fig. 5) taken on February 10, 1955 showed diffuse mottled densities throughout both lung fields with thin-walled cavitation in the upper right lobe. A repeat chest film taken on February 15, 1955 was unchanged. The patient was treated with a sulfonamide, quickly improved, and was discharged. The final diagnosis was chronic lung disease of unknown etiology.

She did well until one year prior to the present admission when she began to have recurrent short episodes of dyspnea and weight loss. Three weeks before admission a chill developed followed by fever, cough, increasing shortness of breath and chest pain. On the day of admission dyspnea was profound and the patient looked moribund. She was without recordable blood pressure or pulse, and was rushed to the medical ward where fluoroscopy, with the patient on a stretcher, revealed a tension pneumothorax on the left and shift of the mediastinal structures to the right. Needle aspiration of air was attempted but it was almost immediately apparent that rubber catheter insertion with water seal drainage was needed. This was done and the patient began to improve. Physical examination on admission otherwise revealed an extremely emaciated Negro woman with inappropriate affect, carious teeth, marked muscle wasting, and marked clubbing of the fingers. A chest roentgenogram taken on admission (Fig. 6) revealed, in addition to the left-sided tension pneumothorax with shift of the mediastinal structures to the right, marked honeycombing with multiple cystic lesions of the right lung. A clinical diagnosis of sarcoidosis was made.

Laboratory work on admission demonstrated a white blood cell count of 4,300 per cu. mm. with 78 per cent neutrophils, 12 per cent lymphocytes and 10 per cent monocytes. The hematocrit was 42 per cent, urinalysis was within normal limits, the serum total protein was 5.9 gm. per cent with 2.8 gm. albumin and 3.1 gm. globulin. The serum electrolytes were within normal limits. Results of tuberculin and histoplasmin skin tests were negative.

The patient initially did fairly well until April 29, 1957 when she had a generalized seizure followed by a semistuperous state and hypotension. At this time it was noted on a chest film (Fig. 7) that a pneumothorax had developed on the right, with about 15 per cent collapse, and a tube was inserted under water seal drainage on this side. The patient again improved. On May 1, 1957 a partial pneumothorax (Fig. 8) on



FIG. 7. Same case. Left lung is almost totally expanded and there is a small right spontaneous pneumothorax.

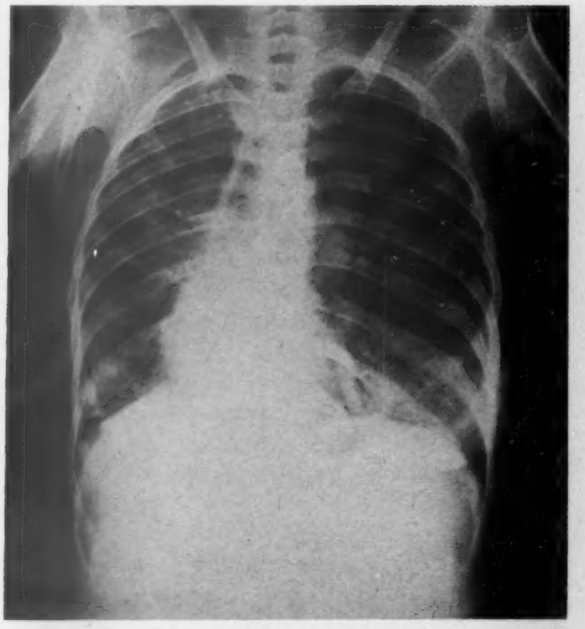


FIG. 8. Same case. Recurrent left pneumothorax with mediastinal displacement. The right lung has completely expanded and the cystic changes are clearly seen.

the left again occurred and a tube was reinserted into the left side of the chest. A liver biopsy was performed on May 16 in an attempt to prove the suspected diagnosis of sarcoidosis. It was negative. On May 20 treatment with hydrocortisone, 300 mg./day, was started and the patient was transferred to surgery where on May 23 a lung biopsy and talc poudrage was performed on the left. The patient withstood the operation well and had no further recurrence of pneumothorax. On June 3, after gradual decrease in hydrocortisone dosage, the drug was discontinued. The patient now complained of shortness of breath which was relieved only by nasal oxygen. On June 12, because of marked hypotension and profound weakness, administration of hydrocortisone, 200 mg./day, was resumed. On this regimen the patient again slowly improved; she was discharged on August 15, 1957. Pathologic examination of the biopsy specimen of the lung demonstrated scattered foci of non-caseating granulomas and pulmonary fibrosis. The patient was again seen on September 13, 1957 when she was brought to the Admitting Office in profound respiratory distress. No blood pressure or pulse was obtainable. She died within a few minutes of admission.

Through the courtesy of the coroner's office, a limited autopsy examination was obtained. Postmortem examination revealed dense adhesions in the left side of the chest, between the parietal and visceral pleura from apex to base, as a result of the previous talc poudrage. On the right there was a pleural effusion of 800 cc. of straw-colored fluid. The lung surface was covered with multiple blebs and smaller obviously cystic areas. The heart was moderately enlarged, with right ventricular dilatation and hypertrophy. Mediastinal lymph nodes, both paratracheal and peribroncheal, were grossly enlarged and revealed non-caseating granulomas on microscopic section. Fungus stains were negative. The lung on microscopic section revealed diffuse honeycombing and cystic dilatation of the alveoli and finer bronchioles. Scattered throughout the lung parenchyma were foci of non-caseating granulomas of the epithelioid type. No granulomatous inflammation was evident in either the liver, spleen, kidneys, ovaries or central nervous system. It was concluded that the mediastinal lymph nodes and pathologic condition of the lung were typical of sarcoidosis.

Comment: Diffuse cystic involvement of the lungs has been poorly characterized in the past; there has been some tendency to group together such conditions, whether localized or generalized, and originating from bronchial or alveolar tissue. Such diffuse cystic involvement may be secondary to bronchial obstruction or to bronchiectasis. There is one variety of thin-walled cysts, varying in size up to 1 cm. and distributed uniformly throughout both lungs, which appears to be of a distinctive nature. Oswald and Parkinson [*21*] described sixteen such cases under the heading of "honeycomb lungs." Their patients followed a distinctive clinical course characterized by recurrent spontaneous pneumothorax, frequently

on alternate sides with progressive ventilatory insufficiency, cor pulmonale and death. In six of their cases pathologic examination was performed. The changes were attributed to xanthomatosis of the Hand-Schüller-Christian variety in one patient, tuberous sclerosis in one patient, two infants had associated biliary cirrhosis, and there were two patients with diabetes insipidus presumably also due to xanthomatosis. However, complete pathologic study was lacking. "Muscular cirrhosis of the lungs," attributed to a formes-fruste of tuberous sclerosis, has also been described in the etiology of this peculiar honeycombing pattern.

The cause of widespread alveolar cysts is unknown. Mechanical factors resulting from acquired disease in the pathogenesis of the cysts may be postulated, but whether they are produced by impeded expiration due to bronchiolar obstruction or to stress in the more normal parts of the lung after widespread alveolar destruction elsewhere is not clear. At any rate, the cysts have a tendency to enlarge gradually as time goes by and eventually to rupture with production of a tension spontaneous pneumothorax.

Spontaneous pneumothorax is mentioned infrequently in the literature as a complication of sarcoidosis. In the case described by Gendel and Luton [*22*], death was apparently due to the pneumothorax, for the patient, after demonstrating typical symptoms and signs including roentgenographic evidence, went into shock and died despite aspiration of air from the chest. Pneumothorax in this case was attributed to bronchial compression by mediastinal and hilar nodes, with resultant emphysematous blebs and probable rupture. The two patients described by Freiman [*23*] both recovered, so the mechanism remains unexplained. In our case spontaneous pneumothorax was of the tension variety, necessitating catheter insertion and water seal drainage. It recurred three times on alternate sides and finally required thoracotomy with talc poudrage. It should be noted that the development of a tension pneumothorax superimposed upon an already compromised ventilatory function was a catastrophic event requiring immediate intervention in the form of tube drainage.

Spontaneous pneumothorax as a complication of pulmonary sarcoidosis may be more common than heretofore realized, and should be considered seriously in any patient with known diffuse pulmonary sarcoidosis in whom progressive ventilatory insufficiency or a shock-like state suddenly develops.

Severe Hemoptysis Secondary to Bronchiectatic Changes of Sarcoidosis. Sarcoidosis is not usually included in the differential diagnosis of hemoptysis but from time to time has been reported as a cause, usually only of blood-streaked sputum [*24*]. There are rare case reports of massive hemorrhage [*25,26*]. These have been thought to be due to bronchiectatic changes occurring with diffuse sarcoidosis. This was true of the following case.

Case IV. E. T. (Hospital No. 19990), a twenty-nine year old Negro woman, was admitted to the D. C. General Hospital on June 21, 1956. About 1950 a cough first developed and the patient had had a chest roentgenogram taken which was abnormal. She was treated for pulmonary tuberculosis by her private physician at two state sanitoriums with isoniazid, para-aminosalicylic acid and streptomycin. Sputums were negative for tubercule bacilli by smear and culture. The patient was subsequently hospitalized at another hospital from August 14, 1953 to September 22, 1953 for sudden shortness of breath and right-sided chest pain. A presumptive diagnosis of far advanced pulmonary tuberculosis was made. She was again treated with antimycobacterial drugs. Her sputums and gastric content examinations were again negative for tubercle bacilli, but her PPD skin test was positive at that time. The patient failed to improve. In January 1954 a cervical lymph node biopsy was performed and the findings were consistent with classic sarcoidosis. Antituberculosis therapy was discontinued. A tuberculin skin test repeated at this time was negative. The patient was again seen elsewhere in September 1955 with a right-sided tension pneumothorax which expanded with closed drainage but recurred when the chest tube was clamped. A right thoracotomy was attempted but hypotension suddenly developed, which responded to the administration of digitalis and prednisone. In November 1955 a right thoracotomy was performed, with apical pleurectomy, imbrication of surface emphysematous blebs, and excision of hilar lymph nodes. Postoperatively the patient had several episodes of hemoptysis. She was discharged in January 1956, improved, and was followed at monthly intervals in the chest clinic. She was dong well and had no complaints when last seen there on June 14, 1956.

Seven days later, on June 21, the patient was admitted for the first time to the D. C. General Hospital because of a moderate hemoptysis. She was treated with sedation, codeine and bed rest. She did well until the fourth hospital day when she had a massive hemoptysis of 800 cc. of grossly bloody material. Her hematocrit dropped to 25 per cent at this time.

Hypotension developed, and 1,000 cc. of whole blood was administered, with improvement in her blood pressure and a rise in hematocrit to 34 per cent. A roentgenogram showed a large cavity in the upper left lobe. On the following day, without any obvious blood loss, hypotension again developed, and it was necessary to administer Mephentermine intravenously to maintain blood pressure. The patient was given another 1,000 cc. of whole blood and a pneumoperitoneum was introduced. On a regimen of vasopressor drugs and weekly pneumoperitoneum, the patient recovered uneventfully.

Laboratory work during her hospitalization showed a white blood cell count of 10,400 per cu. mm. with 68 per cent neutrophils and 32 per cent lymphocytes. Her prothrombin time was prolonged to twenty seconds (control fifteen seconds). The platelet count was 500,000. The urinalysis was within normal limits. Multiple sputums and gastric content examinations were negative for tubercle bacilli by smear and culture. Results of tuberculin skin tests were negative. Multiple films of the chest revealed marked pulmonary fibrosis throughout both lung fields with what was interpreted as a blood pneumonitis in the upper left lung field; this cleared rapidly to reveal a large area of cavitation. (Fig. 9.)

After the patient had recovered sufficiently, pulmonary function studies were carried out. Ventilatory studies demonstrated a restrictive defect of moderate degree. Alveolorespiratory data revealed perfusion with poor ventilation, both consistent with sarcoidosis.

Following a review of these data, it was decided that although the patient could probably tolerate a thoracotomy and resection of the upper left lobe, she probably could not withstand the left pneumonectomy which might be surgically indicated. The patient had advanced fibrotic disease, increasing the likelihood that cleavage planes would be obscured. She was discharged with a final diagnosis of diffuse pulmonary sarcoidosis with secondary pulmonary fibrosis and bronchiectasis.

Comment: It is interesting to note that in addition to severe hemoptysis, this patient suffered a spontaneous tension pneumothorax on a previous hospital admission. In Russakoff's first case [*25*] the patient also had a spontaneous pneumothorax prior to admission for severe pulmonary hemorrhage.

It is apparent that patients with the degree of pulmonary involvement suffered by this patient may experience many of the serious complications attributed to any diffuse lung disease but that prompt and adequate therapy may suffice to enable them to carry on.

Mediastinal Sarcoidosis Presenting with Dysphagia and Horner's Syndrome. Mediastinal granulomatous masses are not usually included in the differential diagnosis of dysphagia and when they are, almost all cases have been attributed to mediastinal tuberculomas [*27*]. A review of the literature in this regard reveals that in many cases tuberculosis has been assumed to be the cause although tubercle bacilli have rarely been demonstrated in the pathologic material examined. In our experience histoplasmosis is the most common proved cause of mediastinal granuloma.

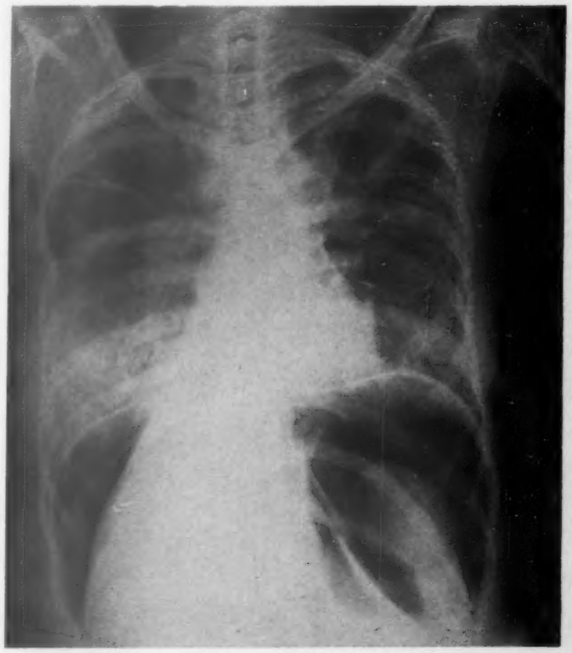


FIG. 9. Case IV. Diffuse pulmonary fibrosis and large cavity in the upper left lobe. A pneumoperitoneum was induced because of severe hemoptysis.

We present the following case as an example of sarcoid granuloma causing extrinsic pressure on the esophagus.

CASE V. F. M. (Hospital No. D-54556), a nineteen year old Negro boy, was admitted to the D. C. General Hospital on May 26, 1951 with a history of sudden development of dysphagia (complete for solid food and partial for liquids) twelve days prior to admission. Associated with this he had noted hoarseness and the need to clear his throat of accumulating viscid secretions. Four days prior to his admission he had been hospitalized elsewhere and a barium swallow had been reported to show almost complete obstruction at the level of the fifth thoracic vertebra. Esophagoscopy revealed no abnormalities except for "posterior esophageal wall edema," the scope being passed 35 cm. from the incisor teeth. The past medical history revealed that he had received a full course

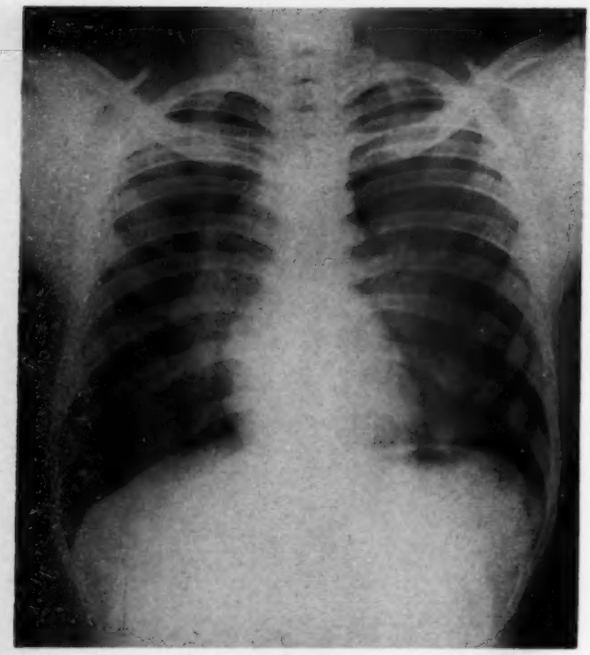


FIG. 10 Case v. Marked bilateral hilar and right paratracheal adenopathy with linear striations extending toward the inner portions of both leaflets of the diaphragm.

of penicillin therapy for syphillis, six months prior to admission.

Physical examination demonstrated a well developed, well nourished young Negro boy appearing in good health. Positive physical findings on admission were confined to several small shotty non-tender lymph nodes in the posterior cervical, epitrochlear and inguinal areas. Laboratory work showed a white blood cell count of 9,950 per cu. mm. The differential count was 75 per cent neutrophils, 5 per cent bands, 17 per cent lymphocytes and 3 per cent monocytes. The hematocrit was 32 per cent. The serum total protein was 8.5 gm. per cent, albumin 4.5 gm. and globulin 4.0 gm. A serological test for syphilis was positive in a 1:8 quantitative dilution. Sputums were negative for tubercle bacilli by smear and culture on three occasions. An electrocardiogram showed upper AV nodal rhythm with a normal axis. A chest roentgenogram (Fig. 10) revealed marked bilateral hilar and paratracheal adenopathy. Roentgenograms of the hands were normal. A barium swallow showed what appeared to be extrinsic compression on the left at the level of the fourth and fifth thoracic vertebra. Examination of the eyegrounds was unrevealing, as was a bone marrow examination. Bronchoscopy and laryngoscopy showed no abnormalities except for profuse secretions of a non-purulent nature in the region of the larynx. Tuberculin in first and second strengths, as well as coccidioidin and histoplasmin skin tests, were negative.

The hospital course was one of gradual improvement. With the administration of atropine, the patient's dysphagia gradually improved. Six days after admission, on a very hot day, the patient was noted to be perspiring on only the right side of his face up to the midline and to have a slight ptosis on the left side. There was no inequality of the pupils. This was felt to represent a partial Horner's syndrome secondary to the superior mediastinal process.

Because of the appearance of the chest roentgenogram and the benign course with gradual improvement, sarcoidosis was suspected and multiple biposy specimens from several sites were obtained in order to avert open thoracotomy. A tonsillar biopsy specimen revealed chronic tonsillitis. The liver biopsy specimen was negative, as was a left axillary lymph node which was reported as chronic lymphadenitis. A gastrocnemius muscle biopsy specimen revealed a single granulomatous nodule, and on the basis of this the diagnosis of sarcoidosis was considered to be proved. The patient continued to improve and on July 17, 1951 was discharged to follow-up by the chest clinic where he continued to do well.

Comment: In our experience as well as that of others, a gastrocnemius muscle biopsy specimen selected at random has been an extremely useful method of obtaining pathologic proof of the presence of systemic sarcoidosis. Since the finding of a granulomatous process involving muscle is an extreme rarity in tuberculosis [*28*], a muscle biopsy specimen positive for non-caseating granulomas has important significance. In the few studies which have been undertaken to show the incidence of positive muscle biopsies in sarcoidosis, Myers et al. reported on four cases [*29*]; Phillips reported four positive results in five [*30*]; and Maurice, five in seven [*31*]. In our experience the incidence of positive muscle biopsies, with specimens taken at random, has been about 10 per cent of the cases in which pathologic proof was otherwise available.

The other features in this case, namely the benign course, the suggestive chest film, negative skin tests and hyperglobulinemia would all seem to fit well with sarcoidosis.

Sarcoidosis of the Larynx. From time to time there have been isolated case reports of sarcoidosis of the larynx [*32–38*] Most of these cases have been relatively benign in that infringement upon the airway was not so severe as to necessitate a tracheotomy. Although tuberculosis was effectively ruled out, special fungus stains had not been performed on the biopsy specimens to eliminate the possibility of involvement of the larynx with chronic disseminated histoplasmosis. As has been pointed out by Israel et al. [*39*] in-



FIG. 11. Case VI. Tomograms of the larynx and trachea showing soft tissue shadows in both laryngeal vestibules and subglottic stenosis.

volvement of the oral cavity and larynx is common in cases of disseminated histoplasmosis, and unless special fungus stains are performed the histopathology may be confused with sarcoidosis. It is for this reason that we include the following case. Of further interest in this report was the regression in the subglottic stenosis and hilar adenopathy on administration of cortisone. It would appear therefore that, although rare, laryngeal involvement with sarcoidosis is but another example of the protean manifestations of this disease.

CASE VI.* M. L., a thirty-two year old Negro woman, was first seen at another hospital on October 2, 1950 because of two verrucous lesions on the upper left eyelid at the inner canthus, and an enlarged left lacrimal gland. A biopsy specimen of the verrucous lesions and left lacrimal gland demonstrated classic sarcoidosis. Roentgenograms of the chest and hands were within normal limits. Minimal hoarseness was present, due to a small polypoid growth discovered on the superior surface of the left true cord anteriorly. This was removed and reported as "tuberculosis versus sarcoidosis; sections showed rounded groups of epitheloid cells, fibrosis and in one section a small area of necrosis." A tuberculin skin test was negative.

The patient received no specific therapy and was next seen in March 1954 complaining of increasing hoarseness for a year and the appearance of new lesions on her face beginning at the right ala nasi. A biopsy specimen from her forehead was reported as sarcoidosis and laryngoscopy again revealed a vegetative lesion between the left true and false vocal cords. She was next seen in June 1956 complaining of hoarseness and obstructive dyspnea at the nasal and laryngeal level. A chest film at this time revealed prominent bilateral hilar and paratracheal lymphadenopathy with clear lung fields. Tomograms of the trachea and larynx in anteroposterior and lateral views (Fig. 11) revealed an increase in soft tissue shadow in both laryngeal vestibules and subglottic stenosis. A tracheotomy was at first refused but when the dyspnea and inspiratory stridor became worse was performed on August 13, 1956. Biopsy of the larynx revealed thickened epithelium, chronic inflammation and submucosal infiltration by densely packed non-caseating granulomas. Fungus stains were unrevealing, as was a histoplasmin skin test and complement fixation for histoplasmosis.

The patient's breathing improved and the tube remained occluded except when she coughed. On November 9, 1956 the tube was removed, only to have severe obstructive dyspnea recur; another tracheotomy was performed on November 12. Administration of prednisone, 30 mg. a day, was instituted, and there was marked improvement. On December 20, the tracheotomy tube was again removed. As prednisone dosage was tapered down to 15 mg./day, slight respiratory distress recurred and the dose was increased to 20 mg./day. On this regimen, the patient

* Reported through the courtesy of Dr. William Trible.

slowly improved and four months after the initiation of prednisone therapy it was discontinued. A follow-up chest roentgenogram taken on May 2, 1957, revealed regression in the size of the hilar and paratracheal lymph nodes.

Comment: The submucosal infiltration which occurs in sarcoidosis has been well illustrated by several observers who have demonstrated the efficacy of a bronchial punch biopsy specimen taken at random at the time of bronchoscopy [*40,41*]. It is unusual for such submucosal infiltration to cause infringement upon the airway but apparently, as in our case, this may occur. The pathological nature of this lesion is basically different from that of tuberculosis or fungus diseases, which have a tendency to caseate and ulcerate the overlying mucosa. Moreover, tuberculosis of the larynx is almost invariably associated with obvious, far-advanced pulmonary lesions with positive sputum, and at least initially involves the posterior portion of the larynx. In our case the subglottic stenosis was due to mechanical blockade and narrowing by redundant granulomatous tissue without ulceration, which responded extremely well to cortisone therapy.

The Difficulty in Distinguishing Diffuse Miliary Pulmonary Sarcoidosis from Miliary Tuberculosis. The following case presented some atypical features not commonly seen in sarcoidosis and which, in the initial diagnostic workup, appeared to weigh heavily in favor of a hematogenous form of tuberculosis. It was not until after several months of antituberculosis therapy, multiple skin testing, multiple cultures for tubercle bacilli and fungi, and biopsy specimens from multiple sites that we considered it safe to exclude miliary tuberculosis from further consideration.

Case VII. P. E. B., a twenty-six year old Negro man, was admitted to the D. C. General Hospital on August 24, 1956 because of progressive shortness of breath of two weeks' duration. He had gotten wet in a storm three weeks prior to admission and two days later had begun to cough up yellow sputum in scanty amounts. Associated with this he had noted headache, fever, pain in the right scapular region and anorexia. He had been seen by his private physician who had prescribed penicillin and tetracycline therapy. He had not improved, and noting progressive shortness of breath and wheezing had sought admission to our hospital. He had been working at a state mental hospital as an orderly where he had been exposed to patients with tuberculosis.

Physical examination on admission revealed a thin, Negro man with a hacking non-productive cough, not appearing seriously ill. The temperature was 101°F.; blood pressure 118/80 mm. Hg; pulse 84; respiration 16. The positive physical findings were: bilaterally injected conjunctivas, enlarged lymph nodes in the supraclavicular and axillary regions, and crackling rales at both lung bases. A chest roentgenogram (Fig. 12) taken on admission revealed a miliary-like finely granular appearance throughout both lung fields. Associated with this there was bilateral hilar lymphadenopathy. Laboratory examination demonstrated a white blood cell count of 8,750 per cu. mm. with 72 per cent neutrophils, 26 per cent lymphocytes and 2 per cent monocytes. The hematocrit was 44 per cent. Urinalysis was within normal limits. Tuberculin and histoplasmin skin tests were negative.

The patient ran a spiking febrile course and reexamination five days after admission revealed the presence of bilateral pleuritic friction rubs. The diagnostic considerations were sarcoidosis, miliary tuberculosis and a fungus infection. In favor of sarcoidosis was the chest film, however, pleural involvement was considered as being unusual for sarcoidosis. Multiple sputums, gastric washings, bone marrow examination, bronchoscopy and bronchial washings were negative for tubercle bacilli and fungi. Examination of a scalene node showed reactive hyperplasia.

On September 20, 1956 the patient had a headache associated with some nuchal rigidity. A lumbar puncture was performed and spinal fluid examination showed 10 lymphocytes. Because of the fear that this represented early tuberculous meningitis secondary to miliary tuberculosis, isonicotinic hydrazide and para-aminosalicylic acid therapy was instituted. On this regimen the patient continued to run a fever with temperatures ranging between 100° and 103°F., and bilateral pleural friction rubs continued to be present. A liver biopsy on September 25 demonstrated non-caseating granulomatous hepatitis. Despite this evidence for sarcoidosis it was decided that it would be too risky to discontinue anti-tuberculous therapy in view of the earlier findings suggestive of an early meningitis. For the following five months during which therapy was continued, multiple cultures, skin testing and complement fixation tests for fungi were carried out, without avail. The patient ran a continuous fever with temperatures ranging between 100° and 103°F., a generalized progressive lymphadenopathy developed and there was a scaly skin eruption involving the neck and chest. He continued to manifest a bilateral pleural friction rub. However, he had lost only 3 pounds, was ambulatory, and showed few signs of toxicity.

Serial chest films displayed a worsening of the granular lung appearance, with conglomeration of densities at both bases and a bilateral pleural effusion. On January 27, 1957 an epitrochlear node biopsy was performed because of continued doubt as



FIG. 12. Case VII. Diffuse miliary densities in both lung fields with larger coalescent nodules at both bases and hilar adenopathy.

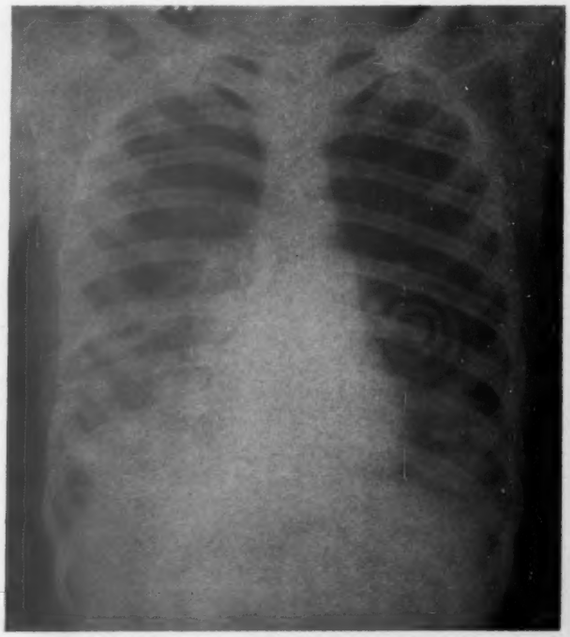


FIG. 13. Same case. Eleven weeks after the start of prednisone therapy there has been marked clearing of the miliary lesions. The basal densities and hilar adenopathy are still present.

to the diagnosis. This was reported as showing granuloma with necrosis. Special stains for tubercle bacilli and fungi were negative. Because of the pathological diagnosis, compatible with tuberculosis, efforts were renewed to elicit a positive culture. These efforts proved fruitless. On April 16, the patient underwent a thoracotomy on the right side, segments of the lung, pleura, skin and muscle being removed. The lung, pleura and skin biopsy specimens revealed noncaseating granuloma, compatible with sarcoidosis.

On April 18 administration of prednisone, 30 mg./day, was instituted and anti-tuberculous chemotherapy discontinued. There was immediate defervescence and marked subjective improvement for the first time in eight months of hospitalization. The patient began to gain weight, noticed improvement in breathing, the bilateral pleuritic pain and friction rubs disappeared. He was discharged to follow-up in the chest clinic on May 8, 1957. During the succeeding six months prednisone therapy has been continued and the patient has steadily improved subjectively and as evidenced on chest roentgenogram. (Fig. 13.)

Comment: The combination of persistent fever, pleocytosis in the spinal fluid, pleural involvement as manifested by persistent friction rubs and later bilateral pleural effusions, an epitrochlear lymph node biopsy displaying oversized zones of focal necrosis in the granulomas, made this patient a complicated diagnostic problem. Much of the evidence seemingly favored a miliary form of tuberculosis. In favor of sarcoidosis were the persistently negative skin tests, the inability to culture tubercle bacilli from numerous sites, and the lack of toxicity or deteriorating course despite progression of lung infiltrations by x-ray, continuous fever and absence of response to antituberculous drugs. When prednisone was initiated there was striking disappearance of all the outward manifestations of the disease. Close follow-up has failed to reveal any evidence of functional disability. This case illustrates the fact that steroids apparently exert their most remarkable results during the cellular proliferative form of the disease, before fibrosis and irreversible lung changes have had a chance to develop.

Pleural involvement in sarcoidosis, and especially pleural effusion, is exceptionally rare. In Longcope and Freiman's classic monograph summarizing 160 cases [*15*] they found only two such cases, and to our knowledge there have been only a few other isolated reports [*6,42,43*].

Migratory Pneumonitis Due to Sarcoidosis. Transient pneumonic infiltrations, usually associated with a benign course and eosinophilia, were originally described by Loeffler in 1932 and again in 1936 [*45*]. The number of recognized

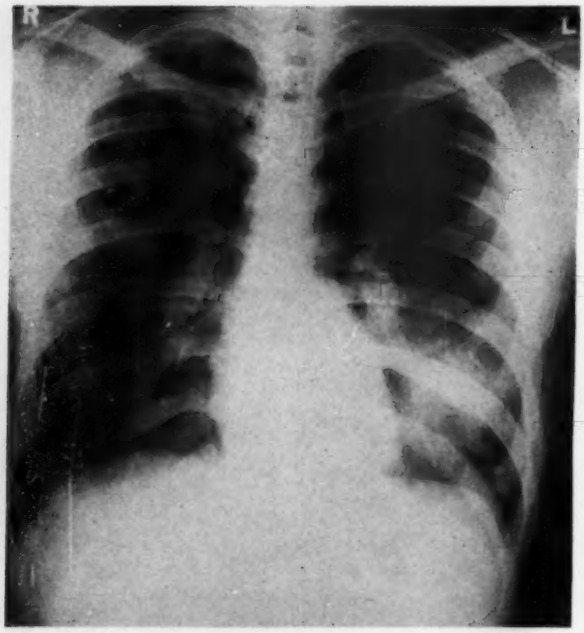


FIG. 14. Case VIII. Bilateral hilar adenopathy, nodular densities and pneumonic involvement at the left base.



FIG. 15. Same case. Two weeks later there has been considerable clearing of the pneumonia at the left base, with a new mottled density in the lower half of the right lung field.

etiologic agents has increased greatly since the allergic background of this syndrome has been known. The exciting factors may be broken down to two basic groups: extrinsic (plant pollens and drugs) and intrinsic (associated with infections such as brucellosis, tuberculosis, amebiasis and intestinal infestations with ascaris, necator, Fasciola hepatica and Ancylostoma braziliense).

Recently we observed a patient who presented with continually shifting pneumonic infiltrations over a three-month period, had generalized lymph node enlargement, had persistently negative skin tests, negative cultures for tubercle bacilli and fungi, followed a benign course, and ultimately came to open thoracotomy with lung biopsy which revealed classic sarcoidosis. With prednisone therapy, complete clearing resulted.

CASE VIII. D. C., a twenty-eight year old Negro (Hospital No. 3524), was first admitted to the D. C. General Hospital on February 10, 1957. His complaints at that time were fever, cough and chest pain. Physical examination was within normal limits except for a temperature of 101°F. His white blood cell count was 3,850 per cu. mm. with 31 per cent neutrophils, 62 per cent lymphocytes and 7 per cent monocytes. Throat and sputum smears and cultures demonstrated no pathogens. His hematocrit, hemoglobin, urinalysis, cold agglutinin titer and chest film were negative. The patient was discharged with a diagnosis of an upper respiratory infection.

He continued to manifest symptoms of sore throat, fever, malaise, cough and occasional fleeting chest pains. Serial chest films demonstrated a migratory type of pneumonic pattern involving both lung fields. Skin tests with tuberculin, histoplasmin and coccidioidin as well as repeated cold agglutinin studies were negative.

One month prior to his second admission generalized lymph node enlargement began to develop. The chest film now showed bilateral hilar lymph node enlargement in addition to the pneumonic infiltrations. (Figs. 14 and 15.) He was readmitted to the D. C. General Hospital on March 25, 1957 because of his continued symptoms and to evaluate the changing roentgenographic picture.

Laboratory work on this admission demonstrated a white blood cell count of 3,800 per cu. mm. with a normal differential. The hematocrit was 49 per cent; urinalysis and serological tests were negative; multiple sputums and gastric washings were negative for tubercle bacilli, pathogens and fungi by smear and culture. The serum total protein was 6.8 gm. per cent with an albumin of 4.3 gm. and a globulin of 2.5 gm. A liver biopsy was negative; however, a scalene node biopsy specimen showed non-caseating granuloma. Bronchoscopy and bronchial washing were negative.

The patient ran a febrile course in the hospital with temperatures ranging up to 102°F. In addition to his previously mentioned symptoms he now complained of arthralgias, and two weeks after admission right pleuritic pain and a pleural friction rub developed.

Because of uncertainty as to the correct diagnosis, the patient was subjected to an open thoracotomy and lung biopsy on May 13, 1957. Pathologic study of the biopsy specimen revealed typical diffuse sarcoid granulomas involving the lung parenchyma, with granulomatous infiltration of the submucosa of a small bronchus. There was round cell infiltration of the pleura but no definite granuloma. On May 22 the patient was discharged on a regimen of prednisone, 30 mg./day. On this regimen subjective symptoms cleared rapidly and his chest roentgenogram (Fig. 16) was within normal limits in two months.

Comment: Although Loeffler emphasized that some cases of migratory pulmonary infiltrations are actually manifestations of tuberculin allergy, there was no evidence in our case that this was so, or that any other etiologic factors of an allergic nature were present. We were left, then, with the diagnosis of sarcoidosis based primarily on the findings of the lung biopsy and the rapid clearing of the chest, as shown on roentgenograms, with the patient on steroid therapy.



FIG. 16. Same case. Two months after the onset of prednisone therapy there has been almost complete clearing of the lungs. The right costophrenic angle is obliterated and the right diaphragmatic leaflet is elevated as a result of the surgical lung biopsy.

COMMENTS

The diagnosis of sarcoidosis is based on a correlation of clinical, radiologic, immunologic and laboratory data supported by histologic evidence of epithelioid tubercles with little or no evidence of caseation. The keystone of the diagnosis rests on widespread organ involvement with few or mild constitutional manifestations. Practically no organ is excluded, and the diverse clinical types are due to the association of lesions in many organs in various combinations. There are few diseases with the protean patterns of sarcoidosis.

Granulomatous processes are in general a host tissue response to a number of bacterial and mycotic organisms, notably tuberculosis and histoplasmosis. They may be produced, as well, by foreign materials and chemicals such as beryllium, and are also associated with hypersensitivity states (Wegener's granulomatosis and so-called allergic granulomatoses). Because of the multiplicity of known agents which may produce a granulomatous lesion, a pathologic diagnosis of sarcoidosis can be rendered only with reservations and after a thorough attempt has been made to rule out other disorders.

The difficulty in establishing a pathologic diagnosis of sarcoidosis has been compounded in recent years by a broadening of the microscopic criteria, and the increased varieties of tissues which are submitted for pathologic interpretation as a result of the needle biopsy technic. Classically, the microscopic picture of sarcoidosis is a diffuse infiltration of an organ by uniform discrete non-caseating epithelioid granulomas with central multinucleated giant cells of either a foreign body or Langhans type, with or without inclusions (asteroid or Schaumann bodies). Frequently the granulomas are cuffed by fibroblasts or hyalinized connective tissue or may show partial hyaline replacement. The adjacent tissues may show little or no inflammatory response. In lymph nodes in particular a para-amyloid or hyaline-like material is frequently found deposited beneath the basement membranes of capillaries and sinusoids. In more recent years, in conformity with clinical impressions, a confluence or coalescence of the granulomas to form nodules with central zones of hyalinization or necrosis has been accepted as compatible with a diagnosis of sarcoidosis. This has made the pathologic diagnosis of sarcoidosis even more difficult because the resemblance of such a picture to an indolent or healing phase of tuberculosis or histoplasmosis, in particular, is so striking that it is frequently impossible to distinguish the processes.

The presence of Schaumann bodies and asteroid inclusions within the giant cells of the granulomas is a feature that is compatible with but by no means pathognomonic of sarcoidosis. Moreover, these inclusions are not present often enough to make them a helpful index of the disease syndrome. The type of necrosis occurring in the center of the sarcoid granulomas is also usually not specific or helpful. It has been suggested that the necrosis in sarcoidosis is a fibrinoid or coagulative variety rather than a caseous type as is seen in tuberculosis. The term caseous necrosis, although a gross descriptive term, has been carried over and is used to describe the microscopic features of the necrotic zones in tuberculosis and other similar disease states. The term implies an acellular necrotic focus which contains granular debris and nuclear detritus, without preservation of cellular detail. The term fibrinoid necrosis, on the other hand, implies a necrotic focus which is somewhat more eosinophilic and fibrillary in nature, with some persistence of previous cellular detail and without the debris seen in the so-called caseous variety. Unfortunately, both pictures may exist in either disease process. The distinction as to type of necrosis has not been helpful to us.

The second development, the wider scope of material made available for pathologic interpretation by the advent of the needle biopsy, has brought even more complex problems to the pathologist. Of necessity, material obtained by needle biopsy technic is so small that the presence of even one or at most several granulomas, with or without minute zones of necrosis, is gratifying. To infer a specific disseminated disease process from these few lesions is beyond the scope of the pathologist. It is impossible, in the first place, to predict that all granulomas proliferating in the patient are of the same type and size as the few obtained at biopsy. It is also a practical impossibility to identify specific organisms by special stains on such minute quantities of material. Even in known tuberculous patients, organisms can rarely be identified in such granulomas. The material, moreover, is usually inadequate for culture. Negative cultures and histochemical tests for bacteriologic and mycotic organisms on these materials do not rule out these processes.

There are a few findings which appear to have some specific connotation for or against a diagnosis of sarcoidosis. The presence of granulomas in the parietal pleural speaks for tuberculosis; the presence of similar lesions in skeletal muscles and salivary glands is compatible with sarcoidosis. Aside from these rules of thumb, the pathologist is best able to assist the clinician by identifying the granulomas, performing special stains to rule out acid-fast and mycotic infections, and culturing material, if adequate amounts are available. When both clinical and pathologic efforts to identify an offending agent are fruitless, a clinical impression of sarcoidosis is justifiable.

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A Myopathy of Boeck's Sarcoid*

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INVOLVEMENT of skeletal muscle in systemic sarcoidosis is not rare. In recent years several reports in the literature call attention to this [*1–3*]. Ragan and his associates have advocated routine biopsy of muscle in cases of suspected sarcoidosis. They believe that muscle may be frequently involved in the process even though this involvement is unaccompanied by any symptoms or clinical signs [*4*]. Myers and his associates have also stressed the point that although involvement of muscle is fairly common, clinical manifestations in muscle are rare [*5*].

Muscle involvement in sarcoidosis can, however, be symptomatic. The symptoms vary from extremely mild to very severe; from slight cramping and aching in muscles to severe pains accompanied by stiffness. Weakness may become marked, with incapacitation and invalidism. Palpable nodules may develop in the muscle. Wasting occurs, especially in the proximal muscles of the shoulder and pelvic girdles. The wasting may be so pronounced in these groups of muscles that the clinical picture of weakness and wasting simulates a "progressive muscular dystrophy" [*2,6*]. In these reported instances, however, the muscular involvement has been part of the generalized process and accompanies clinical manifestations of the disease in other organ systems.

Instances of involvement of the skeletal musculature alone in Boeck's sarcoid are extremely rare [*7,8*]. The present communication is concerned with three such cases seen at The Johns Hopkins Hospital in the past fifteen years.

CASE REPORTS

CASE I. E. G. (J.H.H. No. 260463), presently a seventy-five year old white housewife, has been observed since 1942. Her illness began some twenty years before she first came under observation at the age of fifty-nine years. It has been characterized by intermittent attacks of fever, frequency of urination, agonizing pain in the muscles of the legs, stiffness and swelling of the knees, and progressive wasting of the muscles of the shoulder and pelvic girdle. There was no familial history of muscular wasting or weakness.

At the time of her first admission to the hospital in 1942 the physical examination revealed a mild erythematous blush over the "butterfly area" of the face, an apical systolic murmur, and a barely palpable liver. There was evident wasting of the shoulder and pelvic girdle muscles without fasciculation. The neurological examination was normal except for slightly diminished deep tendon reflexes. Many laboratory examinations were performed at that time. (Table I.) All of these except the muscle biopsy and the Sulkowich test were unrevealing. During her initial hospitalization she had what was thought by some ophthalmologists to be non-granulomatous uveitis of the left eye which spontaneously cleared within three weeks and never recurred. She has had a slow but steady progression of muscular wasting so that now she is confined to her bed. She cannot raise her arms above shoulder level nor walk unaided. Muscular power in the fingers is good.

Periodic recurrences with spontaneous remissions of fever, urinary frequency, and pain in muscle and joints have continued during the time she has been under observation. The findings on physical examination have changed little, except for weight loss and obvious loss of muscular mass. The remaining muscular tissue has a hard, ligneous consistency. Flexure contractures of the elbows and knees have now developed. There are no objective findings in any of the joints.

The patient has taken only aspirin for relief of the pain in muscles and joints. She has consistently refused steroid therapy. She will not permit a picture to be taken. She is examined at about six-month intervals.

CASE II. F. R. (J.H.H. No. 571894), presently a twenty-seven year old Negro, was admitted to the hospital in August 1952 complaining of abdominal cramps, testicular pain, fever, night sweats and weakness of the legs. The patient's father had tuberculosis. At the age of eight years the patient had had meningococcal meningitis which had been treated with sulfadiazine. The physical examination on admission was unrevealing except for enlargement of axillary and inguinal lymph nodes and slight splenomegaly. The muscles of the pelvic girdle and calf were tender

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FIG. 1. Case III. Left, front view of patient. Note the atrophy of shoulder girdle musculature and musculature of the thighs. Right, side view. The atrophy of deltoid, triceps and biceps is particularly noticeable in this view.

and ligneous. He had intermittent fever, night sweats, and such weakness in the legs that he was unable to walk unaided. Defervescence occurred within ten days, and concomitantly the generalized glandular enlargement and weakness disappeared. Many laboratory studies were made but were unrevealing except for elevation of the levels of protein, calcium and alkaline phosphatase in the serum and the findings at biopsy of the gastrocnemius muscle. (Table I.)

The patient returned six weeks later complaining of chills, fever, headache, anorexia, pain in the muscles of the legs and generalized weakness. He had lymphadenopathy, splenomegaly and tender pelvic girdle muscles. Spontaneously in the course of two weeks all symptoms and signs disappeared.

He returned to the hospital in April 1956 complaining of fever, night sweats, pain in the elbows, and exquisite tenderness in the hamstring muscles of the right leg, of one week's duration. He reported at that time that he had been entirely well from the time of his discharge from the hospital in 1952 until the onset of his present complaints. On physical examination there was no associated lymphadenopathy. The hamstrings and gastrocnemii bilaterally were tender to pressure and had a ligneous consistency. Some weakness was present. Neurological examination was normal except for slightly decreased deep tendon reflexes. Again all laboratory studies were unrevealing. There was spontaneous defervescence with subsidence of all symptoms. The patient remains asymptomatic. He is seen at six-month intervals.

CASE III. S. S. (J.H.H. No. 669267), a fifty-seven year old white man, has been observed for four years. He was first admitted to this hospital in 1954 complaining of weakness of his arms and legs; this weakness has progressed over the past fifteen years, and he has had recent difficulty in swallowing.

The patient came from a long-lived family. He had a penile chancer at the age of twenty and had received antisyphilitic therapy then. In 1950 he was given a course of penicillin by his family physician because he was found to have a positive serological test for syphilis. He had had "lightning" pains in the legs before the course of penicillin; after this therapy these gradually subsided. He had no other stigmas of tabes dorsalis.

His illness began insidiously some fifteen years prior to his admission. He first noted some difficulty in climbing stairs. Gradually, over a period of years, the weakness of the legs became so great that he had to support himself with his hands when climbing

TABLE I
LABORATORY STUDIES

Examination	Case and Date of Examination		
	Case I	Case II	Case III
	June 1942	August 1952	May 1958
Peripheral blood examinations:			
Hematocrit (%)	41	41	45
Sedimentation rate (Wintrob) (mm./hr.)	38	29	27
White blood count (per cu. mm.)	6,400	5,300	7,450
Differential count:			
Juvenile forms	.....	.....	5
Polymorphonuclears	67	54	81
Eosinophils	1	7	2
Basophils	.....	.....	.....
Lymphocytes	25	33	9
Monocytes	7	6	3
L.E. cells	Not done	None found	None found
Blood chemical studies:			
Non-protein nitrogen (mg. %)	26	28	40
Fasting blood sugar (mg. %)	78	96	92
Total serum protein (gm. %)	5.8	8.0	8.0
Albumin/globulin (gm. %)	2.0/3.8	4.6/3.4	4.1/3.9
Calcium (mg. %)	9.2	11.5	13.5
Phosphorus (mg. %)	4.3	3.5	3.3
Uric acid (mg. %)	4.0	4.0	9.8
Alkaline phosphatase (Bodansky units)	3.6	8.6	4.1
Bacteriological studies:			
Guinea pig innoculation of gastric aspiration	Negative	Negative	Negative
Blood cultures	Sterile	Sterile	Sterile
Culture of biopsied muscle (routine)	Sterile	Sterile	Sterile
Culture of biopsied muscle (TBC)	Sterile	Sterile	Sterile
Culture of biopsied node	Sterile	Sterile	Sterile
Serological tests:			
Wassermann	Negative	Negative	Positive
Brucella agglutinations	1/40	Negative	Negative
Tularense agglutinations	1/20	1/80	1/20
Heterophil agglutinations	Not done	1/40	1/10
Skin tests:			
Tuberculin	Negative 1/100 O.T.	Negative 1/100 O.T.	Negative 1/100 O.T.
Trichina	Negative	Negative	Negative
Histoplasmin	Not done	Negative	Negative
Urinalyses:			
Specific gravity	1.014	1.024	1.004
Proteinuria	0	0	0
White blood cells/high powered field	1–2	6–8	1–2
Red blood cells/high powered field	3	0	1
Casts/high powered field	0	0	0
Sulkowich test	2 plus	Not done	4 plus
Stool examination	Normal	Normal	Normal

TABLE I (*Continued*)

LABORATORY STUDIES

Examination	Case and Date of Examination		
	Case I	Case II	Case III
	June 1942	August 1952	May 1958
Biopsies:			
Lymph node	No abnormalities	Hyperplasia	No abnormalities
Skin	No abnormalities	No abnormalities	No abnormalities
Muscle: Biceps	Positive*	Not done	Positive*
Pectoral	Positive*	Not done	Not done
Gastrocnemius	Positive*	Positive*	Positive*
Roentgenograms:			
Chest	Normal	Normal	Normal
Hands	Normal	Normal	Normal

* Typical sarcoid granulomas.

stairs. About three years before admisson he noticed an insidious development of weakness in the muscles of the shoulder girdle. Mild dysphagia appeared six months before admission.

On physical examination he appeared to be chronically ill. There was extensive wasting of the shoulder and pelvic girdle muscles. The muscles were gritty and stringy, but non-tender. There was some weakness of both external recti muscles and the muscles of deglutition. At no time were there any fasciculations. The deep tendon reflexes were slightly diminished. No lymph nodes were felt. There was no hepatomegaly or splenomegaly. There was slight impairment of sensation in the lower extremities. The remainder of the physical examination was normal.

Many laboratory studies were performed. (Table I.) The patient consistently had an elevated level of calcium and uric acid, and a consistently low level of phosphorus in the serum. A Sulkowich test was positive on two occasions. These findings together with the changes seen in the muscle biopsy specimen were the only positive laboratory findings.

In 1956 the patient was given an extensive course of cortisone therapy (200 mg./day for three months) without any observable effect upon the disease process. A Cushing-like picture did develop. After cortisone therapy was stopped the patient showed continuing weakness in the pelvic girdle muscles, and more weakness developed in the shoulder girdle muscles. The distal muscles of the arm and the intrinsic muscles of the hand have been and remain unaffected. Dysphagia increased, and salivation became a problem. The patient was started on a regimen of Meticorten® in August 1956 in a dose of 50 mg./day for six weeks. This was tapered over several months to a dose of 10 mg./day. He has been maintained on this medication at this dosage to the present time. No toxic manifestations have appeared. During this time there has been no worsening of the muscular weakness; indeed, the patient feels he definitely is stronger and the physical therapists who evaluate his strength periodically by the subjective method of Kendall [9] report improvement in his strength and in the function of some muscles. The patient continues ambulatory and operates his construction business despite his severe physical limitations. (Fig. 1.)

PATHOLOGICAL FINDINGS

The microscopic appearance of these muscles was quite typical of sarcoid. There was a marked focal inflammatory response separating and destroying muscle fibers. The inflammation was tuberculoid in type, consisting of epithelioid tubercles and giant cells. No caseation was seen. Schaumann bodies and asteroid inclusions were present in some sections. Numerous round cells, mostly lymphocytes, surrounded the tubercles. There was also perivascular round cell cuffing. In the region of the tubercles some muscle fibers were swollen and showed hyalin degeneration. Others were atrophic. The fibers appeared to exhibit focal sarcolemmal proliferation.

The effect of steroid therapy on these lesions was quite marked. The inflammatory response was reduced strikingly. Scarring occurred, without change in the muscle fibers. These changes

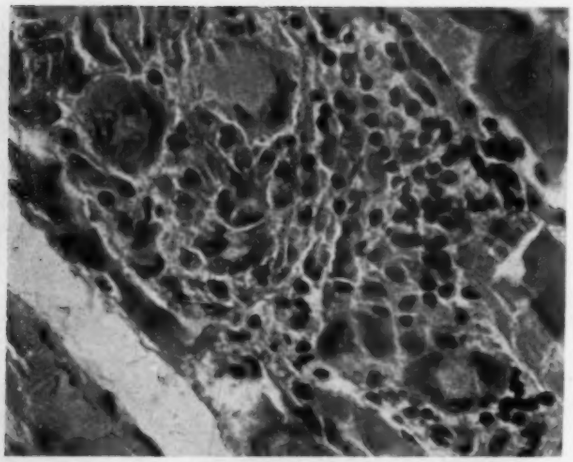


FIG. 2. Case I. Section of biposy specimen, original magnification × 600. Biceps muscle. (Surgical pathology No. 91103.) This shows an organized tubercle with several giant cells separating muscle fibers. A number of lymphocytes surround the tubercles. One focus of atrophic fibers is present.

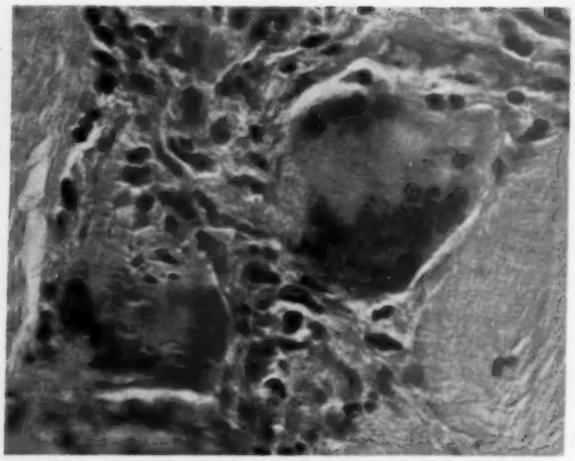


FIG. 3. Case II. Section of biopsy specimen, original magnification × 750. Gastrocnemius muscle. (Surgical pathology No. 52-4111.) This shows a tubercle with two giant cells and surrounding epitheloid cells separating the muscle fibers. The muscle fibers themselves appear normal.

are well illustrated in the accompanying figures which are photomicrographs of the various sections. (Figs. 2 through 5.)

COMMENT ON CASES

Three patients are described who have sarcoidosis which symptomatically appears to be confined to skeletal muscle alone. The onset of the process was explosive in two cases (Cases I and II) and insidious in one (Case III). In each instance the illness began early in adult life.



FIG. 4. Case III. Section of biopsy specimen, original magnification × 100. Biceps muscle. (Surgical pathology No. 54-1946.) Two tubercles are shown separating the muscle fibers. Numerous round cells, mostly lymphocytes, are associated with the tubercles. One giant cell is shown. No caseation or necrosis is present.

None to date has died from the disease. Two are males, one is Negro. In two (Cases I and II) there have been intermittent febrile episodes associated with arthralgias, and exquisite tenderness in the affected muscles. The other patient (Case III) has been free from any pain and from any such febrile episodes.

The process appears to involve many muscles in two patients (Cases I and III), and to be fairly confined to a few muscles in the third (Case II). In those two patients in whom the process is widespread the shoulder and pelvic girdle muscles are involved. In addition, one of these (Case III) has involvement of the striated muscles of the pharynx. In all instances involvement is bilateral and symmetrical.

In two patients (Cases I and III) there has been a slow but steady progression of muscular wasting and concomitant weakness over many years. The third patient (Case II) has shown no residual functional defects following spontaneous remission of the two episodes which he had, although localized muscle wasting is evident clinically and on microscopic examination of the involved muscles.

Clinical laboratory studies on these patients have shown only those changes commonly associated with sarcoidosis. None has been anemic. All have had at some time elevated erythrocyte sedimentation rates. The peripheral leukocyte count has been normal in each instance. One patient (Case II) has shown slight eosinophilia of 5 and 7 per cent on two occasions. Otherwise

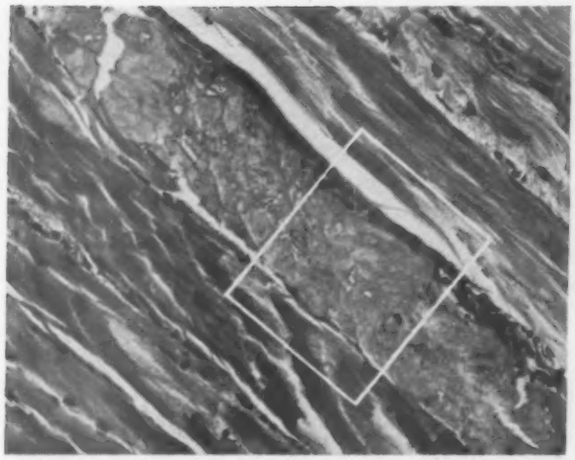


FIG. 5A. Case III. Section of biopsy specimen, original magnification × 300. Biceps muscle. (Surgical pathology No. 54-1946.) An area of a muscle fiber exhibiting hyaline degeneration is seen with high magnification. Note the sarcolemmal proliferation, and the normal striated muscle fibers on each side of the hyalinized fiber.

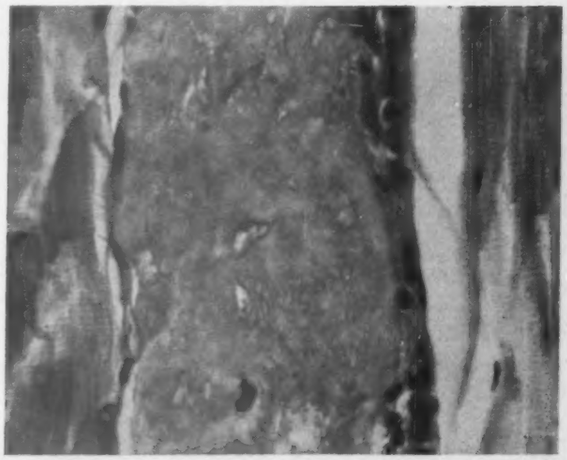


FIG. 5B. Same case. Section of biopsy specimen, original magnification × 750. Biceps muscle. (Surgical pathology No. 54-1946.) Greater magnification of blocked area seen in Figure 5A. Note normal striated fibers on each side of the hyalinized one.

the differential leukocyte counts have been within normal limits whenever determined. In two patients (Cases II and III) cells of the lupus erythematosus type have been looked for but none was found.

The chemical determinations on the serum show that all have elevated globulin levels. In addition, two patients (Cases II and III) have had elevated levels of calcium. One (Case III) had an elevated level of uric acid and another (Case II) of the alkaline phosphatase. A variety of bacteriological examinations were performed in each patient; these revealed no evidence of tuberculosis or brucellosis. Hepatic and renal function studies were normal in each instance, although two of the patients (Cases I and III) at some time in their course had positive Sulkowich tests. Roentgenograms of the chest in these patients have been normal except for pleural thickening at the base in one patient (Case III). There is no bony involvement in any of these cases which can be demonstrated by x-ray films of the hands or feet.

COMMENTS

In 1907 Licharew demonstrated before the Moscow Dermatological Society a seventeen year old girl with palpable nodules in the skeletal muscles [*10*]. In addition she had a skin rash and a palpable liver and spleen. The tuberculin test was negative. It was recognized as lupus pernio.

Bloch in 1914 first demonstrated microscopically sarcoid granulomas in muscles [*11*]. The patient he described had no symptoms referable to muscle. Sundelin in 1925 described a thirty-five year old farmer with palpable nodules in his muscles [*12*]. He had ichthyotic changes in the skin, a uveitis, and bony lesions in his fingers. The lesions in the muscle produced no symptoms. Biopsy showed these to be hard tubercles surrounded by round cells. No caseation was seen. At the time the process was thought to be a hitherto unrecognized affliction of muscle. Subsequently Sundelin reported another similar case and reviewed his first case [*13*]. He recognized both as sarcoidosis involving muscle. There have been many other reports of asymptomatic sarcoid nodules in skeletal muscles [*4–7, 14–17*].

In 1919 Mucha and Orzechowski recorded a patient in whom a picture of muscular dystrophy had insidiously developed over a year's time [*18*]. At the onset she had severe pain in the muscles of her thighs. Weakness of severe degree developed. Later the muscles of the shoulder girdle became involved and generalized weakness appeared. She was thought to have progressive muscular dystrophy but biopsy of the skeletal muscle showed hard tubercles, round cell infiltration and focal atrophy of muscle fibers. A month before death, skin lesions developed which were thought to be typical of Boeck's sarcoid. In 1933 Weinberger described a forty-three year old

man whom he had observed over a period of eight years [*19*]. The patient had intermittent febrile episodes accompanied by generailzed muscular pain, arthralgia, glandular enlargement and splenomegaly. Biopsy of the muscles revealed hard tubercles with round cell infiltration and atrophy of muscles fibers. Muscular wasting progressed; contractures developed. The patient finally became bedridden and died of aspiration pneumonia and cardiac failure. At autopsy there was a cavity in the lower lobe of the right lung, hepatomegaly, splenomegaly and generalized lymphadenopathy. All the skeletal muscles examined were involved by the process. The case was thought to be one of a hitherto unrecognized polymyositis with healed pulmonary tuberculosis. Through the kindness of Professor Herman Chiari material from this case was obtained and re-examination shows that this is quite clearly a case of sarcoidosis. In 1948 Bates and Walsh [*2*] described a twenty-one year old Negro woman who had progressive muscular wasting and weakness. A diagnosis of progressive muscular dystrophy was made. Later in the course of her illness uveoparotid fever developed, and at autopsy there was evidence of widespread involvement of lungs, nodes, liver, spleen, myocardium and skeletal muscle with sarcoidosis. Similar cases of muscular wasting and weakness of fairly severe degree in the course of sarcoidosis have been described by Snorrason [*20*], Krabbe [*21*], Powel [*6*], Warburg [*22*] and Maurice [*23*].

Adams, Denny-Brown and Pearson [*7*] were the first to describe sarcoid involvement of striated muscle alone in the absence of systemic sarcoidosis. They point out in their monograph that sarcoid may cause localized weakness and muscular pain, with progressive atrophy of muscles, in the absence of any signs of systemic disease. The sarcoid granulomas are found within the connective tissue sheaths of the muscle, destroying and replacing the muscle fibers. The muscle mass is thereby reduced and its contractile power weakened. However, they do not report any such case in detail.

In 1956 Ammitzbøll did report such a case [*8*]. His patient was a thirty-eight year old carpenter whom he had observed for four years. The patient had weakness in the muscles of the shoulder girdle accompanied by pain and wasting. This began insidiously. There were no systemic symptoms. On physical examination the patient appeared to be quite normal except for the previously described changes in the muscles of the shoulder girdle. The patient was thought to have progressive muscular dystrophy but as a surprise to all, the biopsy specimen of the muscle showed lesions typical of Boeck's sarcoid. All laboratory studies were unrevealing. The patient's symptoms cleared gradually under treatment with cortisone (65 mg./day) for four months and his strength improved greatly. All symptoms and signs recurred when the cortisone dosage was tapered and its administration discontinued. A second course was begun (12.5 mg./day) and continued for seven months. When treatment was discontinued only a slight temporary "rebound" occurred. The patient appears to be well presently without progression of his disease. He was not receiving treatment at the time of the report and remains well today. This patient of Ammitzbøll resembles the patient in Case III in the present communication in many respects. Their clinical courses appear to be quite similar. Both have shown favorable responses to steroid therapy.

In considering the third type of involvement of muscle with sarcoidosis, namely involvement of striated muscle alone causing progressive wasting and weakness without systemic sarcoidosis, it must be pointed out that none of these cases has, as yet, come to autopsy. It may be that if and when these patients are more completely examined at autopsy systemic sarcoidosis will be found which has produced no symptoms or observable physical signs. This situation is not uncommonly encountered in sarcoidosis.

SUMMARY

Three patients with sarcoid with manifestations apparently confined to skeletal muscle alone are presented. These patients have had recurring bouts of fever, arthralgia and myalgia with associated weakness. Atrophy of the muscles of the shoulder and pelvic girdles is present. Biopsy specimens of affected muscles show hard tubercles characteristic of those seen in sarcoidosis. There is no evidence of systemic disease in any of these cases.

This myopathy is unusual, but may be one of three clinical situations produced by sarcoid when it involves skeletal muscle. Several patients described in the literature as having polymyositis of unknown cause, or progressive muscular dystrophy, on re-examination clearly

have this form of myopathy produced by sarcoid.

Steroid therapy appears to arrest the progression of this myopathy.

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Sarcoidosis*

An Analysis of Forty-Five Cases in a Large Military Hospital

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SARCOIDOSIS, an illness of protean manifestations and unknown etiology, has continued to challenge physicians since the description of the first case by Jonathan Hutchinson in 1875 [*1*]. Skin manifestations were predominant in the early descriptions of the disease [*2,3,4*] and the term sarcoid was coined by Boeck in 1899 when reporting on a patient with a nodular skin lesion which he thought resembled sarcoma [*3*]. In 1914 Schaumann [*5*] advanced the modern concept of sarcoidosis as a widespread disease involving many organs besides the skin. Three years later Schaumann [*6*] established that lupus pernio and Boeck's sarcoid were both manifestations of the same disease, and suggested the term "lymphogranuloma benigna" to distinguish it from malignant granuloma, or Hodgkin's disease. In 1909 Heerfordt [*7*] described uveoparotid fever, but it was only twenty-five years later that this manifestation was recognized as part of the sarcoid syndrome.

After these pioneer studies, as clinicians became more familiar with the disease, the literature grew proportionately, with excellent reports and reviews [*8,9*]. Freiman [*10*] estimated that well over one thousand cases had been reported by 1948. A monumental study, later printed as a monograph which serves as a standard reference on the subject, was published by Longcope and Freiman in 1952 [*11*]. Surveys of the mass chest roentgenograms made by the armed services during World War II uncovered more case material, and excellent articles were written by Ricker and Clark [*12*] and Michael et al. [*13*] on the basis of studies on military personnel.

The present study was undertaken at the Pulmonary Disease Center of Parks Air Force Base Hospital. This unit has served as a diagnostic and treatment center for diseases of the chest since 1953, receiving patients referred from all areas of the United States Air Force. In view of the relatively young average age of the population group from which our patients were drawn, and the relative frequency with which complete physical examinations are made and chest roentgenograms obtained in the military service, it was believed that the present study might further elucidate the early manifestations of sarcoidosis and the diagnostic problems involved.

MATERIALS AND METHODS

Forty-five cases are reviewed in this study, representing all those coded by the records library in the years 1953 through 1957 as sarcoidosis or uveitis secondary to sarcoidosis. All patients from 1954 on were seen by one or more of us. The diagnosis was established histologically in forty cases. In the other five cases the clinical picture was considered sufficiently characteristic to make the diagnosis. Chest and other roentgenograms were available in thirty-three cases at the time the study was undertaken and were reviewed with the staff radiologists. The histopathologic material was interpreted by the Pathology Department and in most cases was reviewed by the Armed Forces Institute of Pathology.

ANALYSIS OF CASE MATERIAL

Only four of the patients were women, a proportion which probably reflects the population group from which these cases were drawn. Of the forty-one men, twenty-five (61 per cent) were Negroes, which compares closely with the 63.5 per cent Negroes from the Army series of Ricker and Clark [*12*]. These authors, noting a 10 per cent Negro population in the Army, calculated an incidence of 0.5/100,000 for Caucasians and 8.7/100,000 for Negroes, or a frequency for Negroes of seventeen times that for Caucasians. Eighty-nine per cent of the male patients were below the age of thirty. (Table I.) Although the figures are too small to warrant

* From the 2349th U.S.A.F. Hospital, Parks Air Force Base, California.

TABLE I
AGE AND RACE OF FORTY-ONE MALES WITH SARCOID

Age (yr.)	Total	Negro	Caucasian
Under 20	5	5	0
20–24	22	13	9
25–29	9	6	3
30 and over	5	1	4
Grand total	41	25	16

TABLE II
SYMPTOMATOLOGY

Symptom	Total	Prominent or Presenting
Pulmonary	32	18
Cough	24	14
Chest pain or discomfort	9	8
Dyspnea	8	6
Hemoptysis	2	2
Weight loss	20	7
Ocular symptoms (e.g., blurred vision)	10	4
Malaise and/or fatigue	10	2
Asymptomatic	9	..
Gastrointestinal (e.g., dysphagia)	5	1
Fever, chills or sweating	5	2
Genitourinary (e.g., calculi, epididymitis)	3	2
Dermatologic (erythema nodosum)	1	1
Lymph node enlargement	2	1
Nasal stuffiness	1	0
Arthralgia	2	1
Hoarseness	1	0

any conclusions, it is of interest that the proportion of cases in Negroes decreases with increasing age, and four of five cases in the thirty and over age group were Caucasians.

The high incidence of residence in the southeastern part of the United States in patients with sarcoid has led to speculation as to the etiological role of beryllium-containing soil [*13*] and forested areas [*14*].

Of those patients whose records included adequate geographical data, 55 per cent had originated from or had long-term residence in the southeastern states. These figures are comparable to those of Ricker and Clark [*12*].

Symptoms (*Table* II). Information on how the disease was discovered was available in forty cases. Eighteen of these patients visited a doctor because of symptoms, but in twenty-two cases (55 per cent) an x-ray film of the chest, taken in connection with a routine physical examination or because of symptoms not related to sarcoid, demonstrated disease. However, on careful questioning only nine of the forty-five patients were entirely asymptomatic. Respiratory complaints predominated, cough being the most frequent symptom; this ranged from a dry "cigarette" cough to one productive of mucopurulent sputum. A "chest cold" was often the reason for the patient seeking medical care. In only two cases was there a significant amount of blood in the sputum and this was the presenting complaint. Weight loss occurred in almost 50 per cent of the cases but was of significant degree in only seven. Blurred vision of rather sudden onset was the most common ocular complaint. Associated symptoms of pain, photophobia, lacrimation and conjunctivitis occurred in ten patients but were the presenting complaints in only four. Fever, chills or sweating were uncommon complaints, and only two patients presented with such symptoms, probably related to acute infection rather than to sarcoid *per se*. Of the gastrointestinal symptoms, dysphagia was the presenting symptom in one case. Testicular pain and swelling was the presenting symptom in one patient and a biopsy subsequently demonstrated granulomatous infiltration of the epididymis. Erythema nodosum occurred in only one of our patients, in contrast to the high incidence (22 per cent) reported by James in England [*16*]. Epitrochlear lymph node enlargement and nasal stuffiness, due to sarcoidosis of the nasal mucosa, were the initial manifestations in one patient.

Physical Findings (*Table* III). The most prominent physical finding was lymphadenopathy, occurring in twenty-five patients. Slit lamp examination of the eyes revealed evidence of uveitis in eleven of twenty-two patients so examined (50 per cent). Objective findings were infrequent as compared to respiratory complaints. Hepatomegaly was present in five patients, but the spleen was palpable in only one. Other less common physical findings were skin nodules in two (erythema nodosum in one), thickened epididymis in two, widened superior mediastinum in two, and nasal mucous membrane thickening in one case of nasal involvement by sarcoidosis. Early clubbing of the

TABLE III
PHYSICAL FINDINGS

Finding	Total
Lymphadenopathy	25
Axillary	13
Cervical	13
Inguinal	9
Supraclavicular	8
Epitrochlear	2
Ocular (e.g., conjunctivitis, conjunctival granuloma) *	4
Pulmonary signs	10
Cardiac murmurs	7
Hepatomegaly	5
Skin nodules	2
Genitourinary (thickened epididymis)	2
Widened superior mediastinum	2
Nasal obstruction	1
Splenomegaly	1
Clubbing of fingers	1

* Slit lamp examination, performed in twenty-two cases, showed evidence of active or inactive granulomatous uveitis in eleven cases, or 50 per cent.

fingers was seen in one patient with diffuse pulmonary sarcoidosis.

Skin Tests. The high incidence of tuberculin hyporeactivity has been noted previously [*12,17,18*] and has been reported to range from 67 per cent (James) to 97 per cent (Ricker and Clark). Our own figure of 79% (thirty-four of forty-three) falls within this range. Only 7 per cent of our patients reacted to 0.0001 mg. of tuberculin (0.1 ml. intermediate strength PPD). Among 737 Air Force personnel under the age of thirty reporting to this hospital for duty, 27 per cent were found to react to intermediate PPD, and among 1,126 persons of all ages results were positive in 37 per cent. Sensitivity to other antigens was also noted to be depressed. Positive reactions to coccidioidin were noted in 7.5 per cent, and to histoplasmin in 10 per cent of patients with sarcoid who were tested. A group of 100 non-tuberculous patients without sarcoidosis, selected at random, revealed 20 per cent coccidioidin reactors and 39 per cent histoplasmin reactors.

Roentgenographic Findings. All forty-five patients in our series had one or more chest roentgenograms, and in only one was the chest roentgenogram within normal limits. This patient was seen one and a half years after an original diagnosis of iritis due to sarcoid. The original x-ray films were not available for review. The diagnosis had been confirmed by lymph node biopsy. Bilateral hilar adenopathy with parenchymal involvement was the most common finding, occurring in twenty-three cases (51 per cent). Adenopathy alone occurred in sixteen cases (36 per cent), parenchymal changes alone in five cases (11 per cent), and a normal chest x-ray in only one. Roentgenographic changes associated with sarcoidosis involving the pulmonary parenchyma have been classified into four types: (1) diffuse and confluent infiltration (Fig. 1), (2) linear type of infiltration usually extending fanwise from the hilum (Fig. 2), (3) disseminated miliary lesions (Fig. 3), and (4) a coarse nodular infiltration. (Fig. 4.) Adenopathy alone, either hilar or paratracheal, or both, was slightly less frequent. Pulmonary changes without obvious adenopathy were seen in only five patients. Evidence of pleural disease, either past or present, was manifest in five patients: blunted costophrenic angle in two, thickened horizontal fissure in two, and equivocal evidence of free fluid in one patient as seen on a lateral decubitus film.

In contrast to the high incidence of bone changes in other series (Longcope and Freiman, 16.4 per cent [*11*]; Stein et al., 17.2 per cent [*19*]; Ricker and Clark, 17.4 per cent [*12*]; and McCort et al., 22 per cent [*20*]) only one of our patients showed changes in hand and/or foot roentgenograms, and these were minimal. This may be a reflection of early recognition of the disease or of the young age of the patients studied. Longcope and Freiman [*11*] remark, ". . . as the reports of cases of generalized sarcoidosis mount in numbers, the actual incidence of bony changes appears to grow less and less." James [*17*] points out that all his patients with bone changes had persistent cutaneous plaques or lupus pernio, and that x-ray films of the bones gave no diagnostic information not already afforded by examination of the skin.

Laboratory Data. Routine blood counts and sedimentation rates were abnormal frequently enough to attach significance to the results. Hemoglobin levels were below 12 gm. in only two patients, but the sedimentation rate was elevated in more than two-thirds of the patients. Half of these were above 20 mm., with a high of 42. The sedimentation rate often returned toward normal as the disease became inactive. Leukocytosis was unusual, even with fever or other signs of active disease, only two patients showing counts of 11,000 per cu. mm. and one

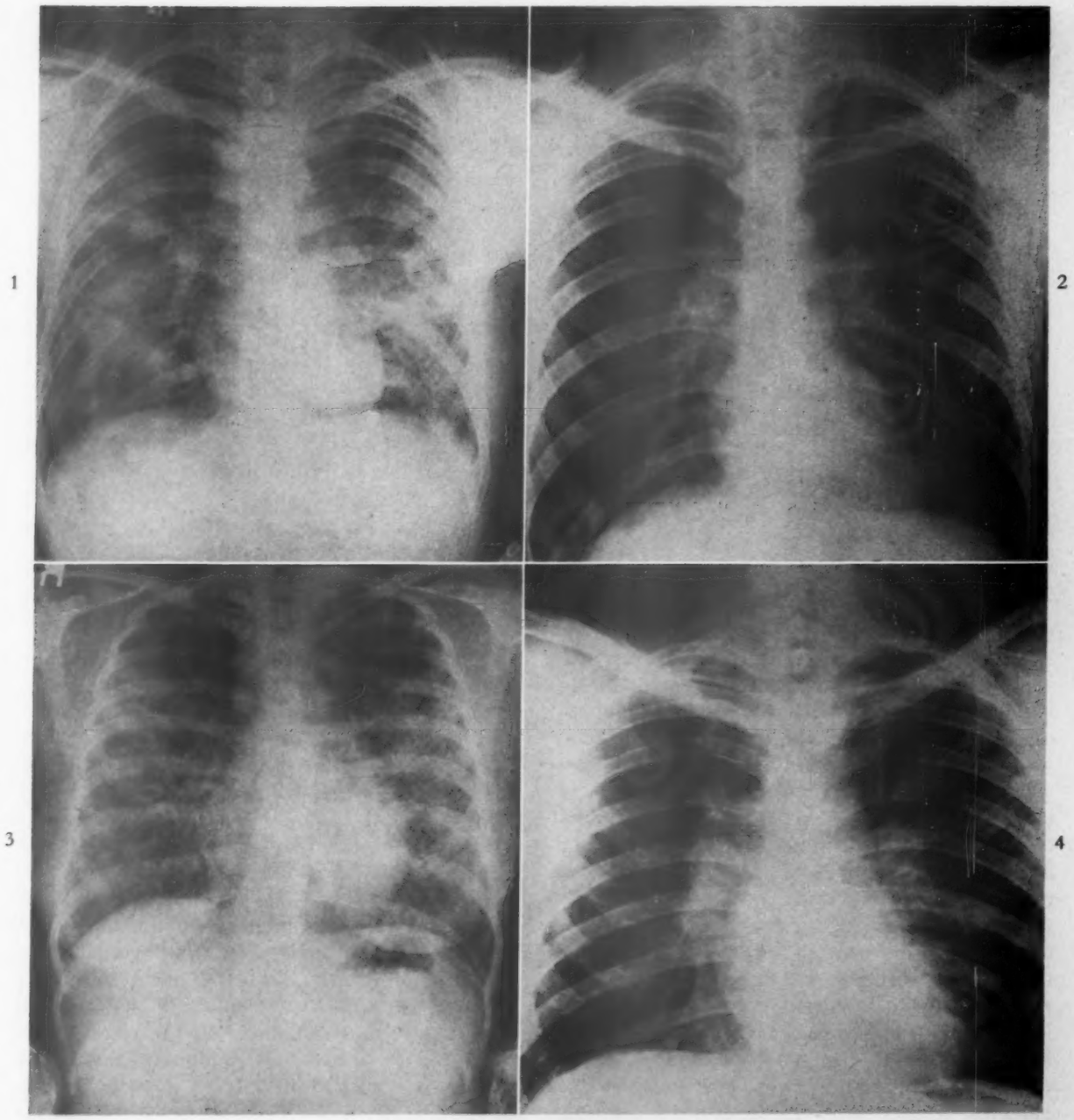


FIG. 1. Chest roentgenogram of a twenty-four year old white man with sarcoidosis, showing bilateral diffuse and confluent infiltrations with only a minimal restrictive ventilatory defect on pulmonary function studies.

FIG. 2. Chest roentgenogram of a twenty-two year old Negro man with sarcoidosis, showing bilateral hilar adenopathy and a linear, reticular infiltration in both midlung fields interpreted as lymphatic obstruction on the right.

FIG. 3. Case I. Chest roentgenogram showing extensive bilateral diffuse miliary infiltrations with sparing of the apices.

FIG. 4. Case II. Chest roentgenogram showing bilateral hilar node enlargement with a nodular pulmonary infiltration.

with 22,000 per cu. mm. Leukopenia (below 5,000 cells per cu. mm.) was found in sixteen patients (36 per cent), with one count as low as 2,400 per cu. mm. No other findings suggesting hypersplenism were found (only one patient had a palpable spleen), although this has recently been reported and the literature on hypersplenism in sarcoidosis reviewed [*16*]. Relative lymphocytosis was common, although of doubtful significance diagnostically. Eosino-

TABLE IV
BIOPSY MATERIAL*

Site	Positive Results (%)	Positive (granuloma consistent with sarcoid)	Negative (or insufficient tissue)
Lymph nodes	62	35	21
Scalene or supraclavicular	62	28	17
Axillary		2	4
Cervical		2	0
Femoral		1	0
Epitrochlear		1	0
Mediastinal		1	0
Liver	60	6	4
Lung		4	0
Conjunctiva (nodule)		1	0
Nasal mucosa		1	0
Epididymis		1	0
Kidney		0	1

* More than one biopsy was performed in some cases.

philia (greater than 5 per cent) was noted in 36 per cent of the patients. Five patients had over 10 per cent eosinophils, with one count as high as 26 per cent; no cause other than sarcoidosis was found for the eosinophilia.

Blood Chemistry. Serum protein determinations were performed in every patient and were found to be abnormal in 60 per cent, twenty-eight showing a decline in serum albumin and/or a serum globulin more than 3.5 gm. per cent. Serum calcium determinations were obtained in thirty-nine patients and values of over 11 mg. per cent were recorded in eleven; five of these values were greater than 11.5 mg. per cent, with a high of 15. Serum phosphorus levels, when determined, were normal, serving as a differential diagnostic point from other conditions producing hypercalcemia. Urinary calcium studies were performed in too few patients to draw definite conclusions.

Miscellaneous Laboratory Data. Liver function tests were performed in twenty-one cases, one or more abnormalities being found in eleven patients. Most of the abnormalities were in the flocculation tests. Serum alkaline phosphatase levels, considered by many to be of diagnostic value in sarcoidosis, were elevated in only three of eleven cases in which the determination was made. One patient with a positive liver biopsy had a normal serum phosphatase level.

Renal function was very seldom impaired as measured by the usual parameters, renal insufficiency being one of the serious but infrequent complications of generalized sarcoidosis. One very ill patient with hypercalcemia and renal insufficiency recovered spontaneously.

Cardiorespiratory Function. Pulmonary function studies, consisting of chest fluoroscopy, timed and total vital capacity, and in some cases maximum breathing capacity, were performed in twenty patients. In ten the results were normal; in the remaining ten mild to moderate restrictive ventilatory defects were found. Pulmonary insufficiency with cor pulmonale, one of the most serious of the complications of sarcoidosis, was not encountered in our series, even in the face of extensive changes on x-ray examination.

Electrocardiograms were obtained in twenty-four patients and found to be abnormal in eight: three showed incomplete right bundle branch block, one of these also had non-specific ST segment changes; two showed non-specific T wave changes; one showed transient ST segment elevations in leads I, AVL and V_3-V_6; and one showed a transient first degree heart block. Only one showed changes suggestive of right ventricular hypertrophy. Without histologic evidence of myocardial changes, one can only conjecture on the presence of sarcoid involvement of the heart. An excellent review of myocardial sarcoid, emphasizing the frequency of conduction disturbances, was recently published by Peacock et al. [*21*].

Biopsy Material (*Table* IV). Histopathologic evidence of non-caseating granuloma, with inability to demonstrate organisms by acid-fast, fungus or other special stains, while not pathognomonic, is usually sufficiently characteristic to confirm the diagnosis of sarcoidosis when correlated with the clinical picture. A total of seventy-four biopsy procedures was performed, forty-eight of which yielded diagnostic material. With few exceptions, lymph node biopsy was the initial procedure utilized in an attempt to obtain a tissue diagnosis. Of fifty-six such biopsies thirty-five (62 per cent) were positive. Figure 5 shows a typical granulomatous reaction. Scalene fat pad dissection was performed when there were no significantly enlarged nodes, or if the initial tissue was non-diagnostic. In contrast to other intrathoracic diseases, sarcoid gave a high percentage of positive biopsies [*22*]. It is interesting also that, regardless of the presence or absence of palpable adenopathy,

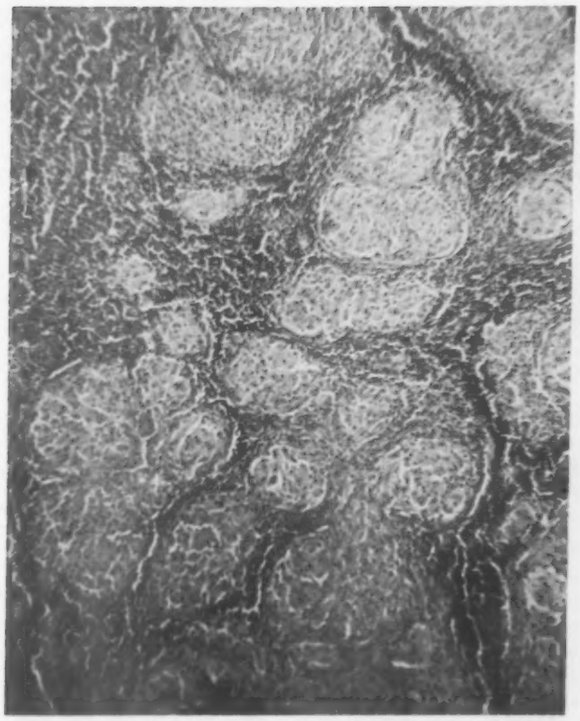


FIG. 5. Left scalene fat pad biopsy showing typical granulomatous reaction in a lymph node, almost completely replacing the normal tissue architecture.

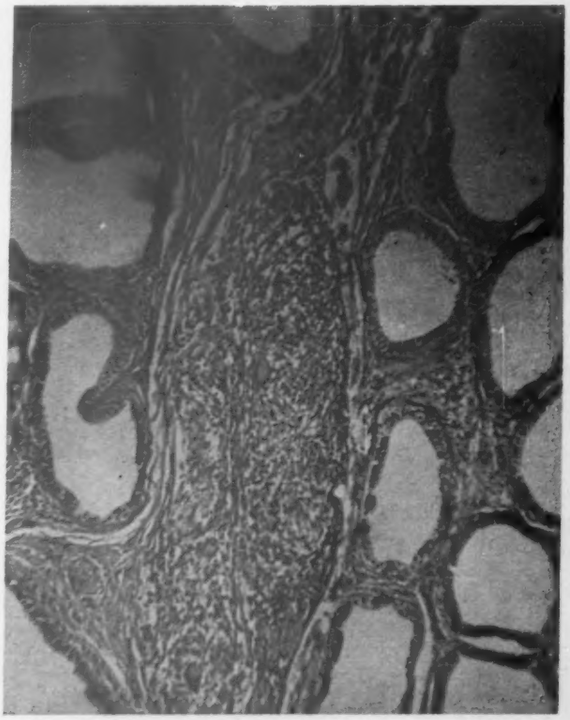


FIG. 6. Section of the left epididymis showing normal tubules with a central granulomatous area, no caseation.

the diagnostic yield was the same. Multiple biopsies were necessary in a number of patients.

More recently, stimulated by the earlier work of Klatskin and Yesner [*23*], and of Nelson [*24*], liver biopsy was used as the initial procedure to obtain tissue for pathologic examination. Klatskin obtained positive biopsy specimens in fifteen of twenty patients; eleven of these fifteen patients had hepatomegaly of a soft, non-tender nature. Nelson obtained eleven positive specimens in sixteen attempts, or 73 per cent; in six of the eleven patients previous biopsies of the lymph nodes were negative. In our own series, liver biopsies were positive in six patients and negative in four including one patient in whom no tissue was obtained. Many authors have emphasized the risk of performing needle biopsy of the liver. However, as Zamchek [*25*] points out in a review of 20,016 needle biopsies of the liver, the true mortality was 0.085 per cent, less than 1:1000, and "the proper use of needle biopsy can save many lives by permitting early diagnosis and prompt institution of correct medical or surgical therapy." Of the cases reviewed, there were no deaths from liver biopsy in patients with actual or suspected sarcoidosis. We are of the opinion that more widespread use of this procedure in the diagnosis of sarcoidosis should be made, since it is a simple bedside procedure, with minimal risk when performed by qualified personnel. The procedure will also yield diagnostic tissue as frequently as does lymph node biopsy.

Lung biopsy was performed in four patients with diffuse pulmonary disease in whom conditions other than sarcoidosis were suspected. All had had previous negative prescalene fat pad biopsy. Biopsy specimens of the lung were positive in all cases. Other biopsy sites were selected to confirm unusual manifestations of the disease in our patients, such as a conjunctival nodule, nasal mucosa and epididymis. (Fig. 6.)

Treatment and Course (*Table* v). Thirty-five of the forty-five patients received no definitive therapy. Twenty-three were essentially asymptomatic, while the other twelve untreated patients had significant complaints. Twenty-seven exhibited no change in symptoms or findings during observation. Three patients had a restrictive ventilatory defect and were separated from the service, and thus lost to follow-up. Eight men showed spontaneous improvement: disappearance of cough in two, improvement in four as seen on chest roentgenogram, hoarseness disappearing in one, and a spontaneous remis-

TABLE V
TREATMENT AND COURSE

Data		Improved	Unchanged	Worse
Patients Not Treated (33)*				
Asymptomatic	16	1	15	
Symptoms (most significant)	17			
Weight loss	7	7		
Dyspnea	4	4		
Cough	4	1	3	
Hoarseness	1	1		
Blurred vision	1	1		
Patients Treated (12)				
Ocular and Systemic steroids	6	3	2	1
ACTH and cortisone (plus eye surgery in one)	4	2	1	1
Cortisone	1		1	
Prednisolone	1	1		
Systemic cortisone alone	5	3	1	1
Ocular cortisone alone	1	1		

* Figures in parentheses represent total number of patients.

sion of hypercalcemia and renal insufficiency in the fifth patient.

Ten patients received corticosteroid therapy. In one, ocular application of steroids alone resulted in a remission of active iritis, with return of normal vision and no recurrence after cessation of medication. Three patients received cortisone systemically only; one was improved, one unchanged, and one worse. Six patients received steroids both systemically and by local application to the eyes, the former usually being added to the regimen after local therapy was unsuccessful. Four of these received ACTH and cortisone, with improvement in two, no change in one, and worsening in the fourth. One patient given cortisone and ocular application of steroids had a mild, restrictive-type ventilatory defect and showed no change after six weeks of therapy. The one patient receiving prednisolone, and cortisone directly to the eye had a remission of active uveitis.

With so small a number of cases it is difficult to draw firm conclusions about the results of therapy. However, we believe that topical use of steroids should be the initial therapy for all patients whose main or sole disability is uveitis. If local corticoid administration is ineffective, systemic hormones should be added to the regimen. Beneficial results should be obtained in most cases. For the very ill patient, intravenous ACTH or systemically administered corticoids seem to be the therapeutic agents of choice. Unless the ventilatory defect is moderate to severe, or progressing, the danger of producing pulmonary fibrosis outweighs the possible benefits to be derived from steroids [*27*]. In view of the spontaneous remission of hypercalcemia and renal insufficiency in one of our patients, one must re-examine this indication for the use of steroids. With a disease manifesting such exacerbations and remissions as does Boeck's sarcoid, treatment should be used only to suppress inflammation which would cause irreparable damage if allowed to continue.

COMMENTS

From an analysis of the foregoing data certain basic points are apparent. Sarcoidosis is usually detected early in its course in military personnel, often when it is apparently asymptomatic, by means of a routine chest roentgenogram. Hilar adenopathy with or without parenchymal changes is the most common finding pointing to the diagnosis. The greatly increased incidence in Negroes was again noted. Other than respiratory and ocular complaints, the symptoms are vague. There is a paucity of physical signs, even lymph node enlargement being non-specific. In addition to the abnormal chest roentgenogram, other laboratory findings include hyperglobulinemia, hypercalcemia and, not infrequently, leukopenia, with relative lymphocytosis and eosinophilia. Some of the more interesting and unusual facets manifested by our patients are illustrated in individual case reports.

CASE REPORTS

CASE 1. F. V., a twenty-five year old Irish female dependent, was transferred to Parks Air Force Base Hospital on May 28, 1956, for investigation of a pulmonary infiltrate. In January 1953 a roentgenogram of the chest revealed a diffuse pulmonary infiltrate. She was then entirely asymptomatic. In September 1953 a child was born uneventfully. In January 1954 studies including skin tests for tuberculosis, bronchoscopy, and guinea pig inoculation were performed, and all were said to be negative. In January 1955 biopsy specimen from a right supraclavicular lymph node was obtained but there was insufficient tissue for interpretation. Following this a liver biopsy was performed and was said to be negative. There were no cardiopulmonary symptoms, no contact or family history of tuberculosis, or exposure to noxious agents. At the time of admission the patient was five months' pregnant, with five previous pregnancies delivered uneventfully, the latest in November 1955.

Physical examination showed a small but well developed, well nourished, white woman in no distress, with normal vital signs. The entire examination was within normal limits except for a grade 1 precordial systolic murmur, and uterine enlargement consistent with a four months' pregnancy.

Laboratory data showed a negative serological test for syphilis, a white blood count of 8,300 per cu. mm. with a normal differential, and a hemoglobin of 12.5 gm. per cent. The corrected sedimentation rate was 31 mm. The urine was normal with concentration to a specific gravity of 1.026. The blood urea nitrogen was 11.8 mg. per cent. The tuberculin skin test (old tuberculin, 1:100) was 1 plus. The serum calcium was 10.5 mg. per cent and the phosphorus 3 mg. per cent. The serum albumin was 1.1, globulin 5.5 gm. per cent. Chest roentgenogram (Fig. 3) showed an extensive diffuse miliary infiltrate bilaterally.

The patient remained completely asymptomatic and afebrile during hospitalization. Because of the necessity of making an accurate diagnosis as quickly as possible, and in view of the negative scalene and liver biopsies in the past, it was elected to perform lung biopsy. On June 12, 1956, an excisional biopsy of the middle lobe of the right lung was performed. Histologically, extensive granulomatous changes were found. (Fig. 7.) Cultures of the surgical specimen for acid-fast bacilli and fungi were negative. Postoperatively, the patient continued to be asymptomatic and was discharged and cleared with no functional impairment. No therapy was prescribed. The diagnosis was sarcoidosis of the lung.

Comment: In this patient, extensive pulmonary infiltration was noted in chest roentgenograms for at least three and a half years, with no functional impairment, even with the added strain of repeated pregnancies. The extensive involvement histologically, in contrast to absence of clinical symptoms, is particularly characteristic of sarcoidosis. This is in contrast to other granulomatous processes involving the lung, such as tuberculosis or berylliosis.

CASE II. J. R., a thirty-one year old Negro man, was transferred to Parks Air Force Base Hospital on October 1, 1956, for evaluation of sarcoidosis. He was originally hospitalized on August 15, 1956, with a two-day history of a painful swollen left testicle and tender red nodules on the medial aspect of the right leg. At that time urine culture showed Aerobacter aerogenes. Broad-spectrum antibiotics, ice packs and a suspensory relieved the testicular symptoms, leaving a residual non-tender epididymal thickening. The skin nodules gradually disappeared.

A two-year history of frequent "chest colds" with non-productive cough and tightness in the chest,

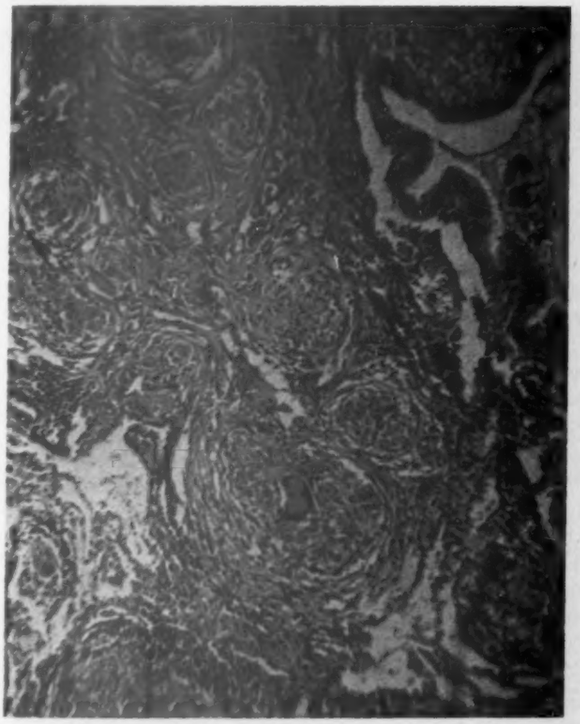


FIG. 7. Histopathologic section of the right middle lobe showing extensive infiltration with granulomatous disease, typified by small non-caseating tubercles. In addition, a great deal of fibrosis is present.

and a four-month history of moderate but progressive exertional dyspnea was elicited. However, a chest roentgenogram and electrocardiogram taken two weeks prior to hospitalization were said to be normal. In the three months preceding admission the patient's weight fell from 180 to 155 pounds. No contact with or family history of tuberculosis was elicited.

During the initial hospitalization a chest roentgenogram showed bilateral hilar adenopathy. Serum proteins, serum calcium, liver chemical studies and roentgenograms of the hands and feet were normal.

The patient had blurred vision in the left eye, was found to have evidence of iritis, and was transferred to a larger facility. There tuberculin (PPD Nos. 1 and 2), coccidioidin and histoplasmin skin tests were negative. The serum total protein was 7.1 gm. per cent, albumin 2.9, globulin 4.2 gm per cent. The serum calcium was 11.5 mg. per cent. Pulmonary function studies showed normal oxygen saturation with no change after exercise, a maximum breathing capacity of 101 per cent of normal, and a vital capacity of 84 per cent (64 per cent in one second, 82 per cent in three seconds). On September 10, 1956, biopsy specimen of a right scalene node showed granulomatous changes. Mydriatics and hydrocortisone eye drops were administered to the left eye, and the patient was transferred to the Parks Air Force

Base Hospital. At this time the patient complained of pain in the left subcostal region and in the left upper quadrant of the abdomen, a mild non-productive cough and blurred vision.

Physical examination revealed a well developed, well nourished Negro man with normal vital signs. The left pupil was dilated (atropine). There were many small shotty non-tender firm and rubbery lymph nodes in both axillas and groins. The chest was clear and the heart was normal. The abdomen showed a tender palpable spleen tip. There was thickening and nodulation at the inferior pole of the left epididymis.

Laboratory data showed a white blood count of 5,600 per cu. mm. with a normal differential, but repeat counts were as low as 3,700 per cu. mm. with up to 66 per cent lymphocytes. The platelet count was 210,000 per cu. mm. The hemoglobin was 14.6 gm. per cent and the corrected sedimentation rate was 22 mm. on admission, falling to 8 at the time of discharge. The urine was normal, with concentration to specific gravity 1.030. The urine Sulkowich reaction (while the patient was eating a low calcium diet) was repeatedly 3 plus, but the twenty-four-hour quantitative calcium excretion was 290 mg. Phenolsulfonphthalein excretion was 45 per cent in fifteen minutes, with a total of 75 per cent in two hours. Serum calcium determinations were 10.1, 11, and 10.6 mg. per cent and the serum phosphorus was 2.6 mg. per cent. The serum albumin was 3.3 gm. per cent, globulin 3.8 gm. per cent. Skin tests for tuberculosis (old tuberculin 1:100), coccidioidomycosis and histoplasmosis were negative. Bromsulfalein retention was 11 per cent and 5 per cent on two occasions. The cephalin flocculation test, serum cholesterol and alkaline phosphatase were normal. A chest roentgenogram showed bilateral hilar adenopathy with a nodular pulmonary infiltrate. (Fig. 4.) Roentgenograms of the hands and feet were within normal limits. An electrocardiogram revealed no abnormalities. Chest fluoroscopy and vital capacity showed normal pulmonary function.

After the first week of hospitalization, pain in the left upper quadrant disappeared and the spleen was no longer palpable. A tender lymph node at the angle of the right mandible appeared but responded to analgesics and local heat. Roentgenograms of the jaw, particularly for salivary calculi, were within normal limits. An ophthalmologic consultant found evidence of active uveitis in the left eye. After two months of cycloplegics and cortisone eye drops, the patient was found to have inactive uveitis with vision correctible to 20/20 in the right eye and 20/20−2 in the left. There was no flareup of uveitis two weeks after all local therapy was discontinued. A dermatologic consultant found no evidence of residual skin lesions. A urological consultant confirmed evidence of epididymal thickening and on November 1, 1956, a biopsy of the left epididymis was taken. The specimen showed epitheloid granulomas compatible with sarcoid. (Fig. 6.) The patient was returned to full duty, asymptomatic, with no limitation of his functional capacity.

Comment: Widespread sarcoidosis was present in this patient, with definite involvement of lymph nodes, lung, eye and epididymis, and probably the liver and spleen. Despite this, the patient had a spontaneous remission of his disease, receiving only steroids locally for his ocular involvement. On the basis of a positive urine culture for bacteria, involvement of the epididymis was originally attributed to infection. However, the histologic picture of granulomatous changes points to sarcoid involvement of the epididymis.

Case III. C. C., a twenty-two year old Negro man born in rural Mississippi, was admitted to the Parks Air Force Base Hospital for the second time on November 29, 1956, for re-evaluation. He had been well until August 1953 when he noted weight loss, wheezing and decreased vision. An x-ray examination of the chest at that time revealed bilateral hilar adenopathy. He was hospitalized and found to have bilateral conjunctivitis and iritis, a precordial systolic murmur, hepatomegaly and massive hilar adenopathy. An ophthalmologist found active granulomatous uveitis bilaterally, prescribed atropine drops and transferred him to this hospital. Physical examination, slit lamp examination and chest roentgenogram confirmed the previous findings.

Initial therapy consisted of local cortisone eye drops and atropine. However, on this regimen the uveitis progressed. The patient was then given oral cortisone, 600 mg. daily initially, gradually tapered to 300 mg. per day for three months. There was great improvement in both the eye status and the chest roentgenogram. Because of a marked Cushingoid appearance and psychoneurosis, the dosage of steroids was further tapered, but within a few weeks the clinical and x-ray findings recurred. Steroids were reinstituted at the previous maintenance levels, with reversal of ocular signs and symptoms.

In February 1954, however, there was a worsening of the ophthalmologic status. Vision was 20/200 in the right eye and 20/400 in the left, and secondary cataracts developed. With increase in steroid dosage the uveitis was suppressed, but vision continued to diminish and the study of Braille was begun. In mid-May, the intraocular tension rose to 56 mm. Hg in the left eye. On May 25, 1954, transfixation of the iris with collapse of an iris bombe was performed, with return of the intraocular tension to normal. A further increase in tension necessitated a basal iridectomy on June 2, 1954, for relief. Following this,

tension returned to normal and there was no further activity of the uveitis. The dosage of cortisone was gradually decreased, with complete discontinuation of steroids by mid-August. Within one week, an iris bombe developed in the left eye, but intraocular tension remained normal. The ophthalmologic picture stabilized, with vision in the right eye 2/400 and light perception in the left eye. Slit lamp showed low grade uveitis bilaterally with an early cataract on the left. No further eye surgery was thought to be indicated and the patient was retired from the Air Force.

At the time of readmission in November 1956, the patient complained of lethargy and vague pain in the flank. He had not worked in the interim but had noted improvement in his vision. He had not received any therapy.

Physical examination revealed a mild Cushingoid facies and abdominal striae. There was no adenopathy or hepatosplenomegaly, the heart and lungs were normal, and the skin was clear.

Laboratory data showed a white blood count ranging from 4,250 to 7,400 per cu. mm. with up to 68 per cent lymphocytes. The hemoglobin was 16 gm. per cent and the corrected sedimentation rate was 3 mm. The serum albumin was 2.8 gm. per cent, globulin 3.3 gm. per cent. The cephalin flocculation, thymol turbidity and alkaline phosphatase tests were normal. The blood urea nitrogen was 15 mg. per cent. The urine was normal. Phenolsulfonphthalein excretion was 69 per cent in fifteen minutes, with a total of 76 per cent in two hours. The urine Sulkowich reaction was one plus, and the serum calcium was 12.6 mg per cent, decreasing to 10.8 mg per cent. Histoplasmin and coccidioidin skin tests were negative, but tuberculin testing showed a two-plus reaction to PPD No. 2. A chest roentgenogram showed minimal hilar adenopathy on the left with clear lung fields. X-ray examination of the hands was normal. An electrocardiogram was normal. The vital capacity was 5 L. (110 per cent of predicted). Chest fluoroscopy showed normal pulmonary ventilation. Ophthalmologic evaluation revealed inactive uveitis bilaterally. Vision in the right eye was 20/80 (corrected); he was blind in the left eye.

During hospitalization the patient became asymptomatic. The patient's vision had improved since 1954 so that he was now able to read with corrective glasses.

Comment: This case represents the most serious complication of sarcoid in our series: severe ocular involvement, with blindness in one eye despite heavy steroid dosage and eye surgery. The advanced ocular damage regressed to the point where vision in one eye was partially restored after treatment was discontinued. The systemic manifestations of the disease, particularly the hilar adenopathy, reverted to normal, as has been reported in the course of hilar node sarcoidosis [*26*].

CASE IV. J. C., a twenty-two year old white man born and raised on an Ohio farm, was admitted to Parks Air Force Base Hospital on August 19, 1954, for investigation of a chest roentgenogram revealing abnormalities found on separation physical examination. The patient was well until three weeks prior to admission when mild productive cough, headache, fever and weakness developed, with tightness and wheezing in his chest two days before admission. There was a 22 pound weight loss in the three weeks preceding hospitalization. No family history or contact with tuberculosis was elicited. He had not been exposed to agents noxious to the lung. There was a questionable history of kidney infection five years previously.

Physical examination showed a well developed, well nourished white man in no distress. The vital signs were normal. Except for a slight expiratory wheeze in the right side of the chest and an increased pulmonary second sound, no abnormal physical findings were present.

The hemoglobin was 13 gm. per cent. The white blood count was 11,000 per cu. mm. with a normal differential, and the corrected sedimentation rate was 25 mm. A serological test for syphilis was negative. A sputum culture showed normal flora. The serum albumin was 3.6 gm. per cent, globulin 3 gm. per cent. Bromsulfalein retention, bilirubin, prothrombin time, thymol turbidity, cholesterol and alkaline phosphatase tests on the blood were all within normal limits. An electrocardiogram was normal. Chest roentgenogram showed bilateral hilar adenopathy with a diffuse patchy infiltrate. Skin tests for tuberculosis, histoplasmosis and coccidioidomycosis were negative in all strengths. Two lupus erythematosus preparations were negative. A bone survey, including the hands and feet, was negative. The serum calcium was 15 and 13.5 mg. per cent. Biopsy specimen of a right scalene node was obtained and this showed a granulomatous reaction compatible with sarcoid. Right renal biopsy revealed only perinephric fat and fibrous tissue. Cystoscopy and retrograde pyelography were within normal limits. Repeat x-ray films of the chest showed partial resolution.

The patient was given a month's convalescent leave, and on returning re-evaluation of his renal status showed gradual improvement. Repeat chest roentgenogram showed only prominent bronchovascular markings. Except for a transient episode of abdominal pain and vomiting, the patient remained asymptomatic and afebrile. Since the patient's four-year enlistment in the Air Force had expired, he was separated from the service and consequently lost to follow-up.

Comment: The renal insufficiency with azotemia in this case, which was reversible without antibiotics and accompanied by hypercalcemia which returned toward normal, was probably a manifestation of generalized sarcoidosis. Positive urine cultures for hemolytic Staphylococcus albus probably represented contaminants, since smears from the bladder and both ureters taken at the time of cystoscopy were negative. The simultaneous improvement in renal function and regression of pulmonary disease without steroid therapy in this case indicates a need for more critical evaluation of the role of steroids in sarcoidosis with renal insufficiency [*27*]. Further studies on calcium metabolism in sarcoidosis, and the effect of steroids on hypercalcuria also are needed [*28*].

SUMMARY AND CONCLUSIONS

A group of forty-five patients with sarcoidosis is reviewed and the salient features analyzed. For the most part these were young, otherwise healthy military personnel whose course was relatively benign. In the few more protracted and serious cases, ocular manifestations predominated and presented the most cogent reasons for steroid therapy. Three patients were medically separated for ocular disability; two continued to have active iritis and/or uveitis despite continuation of systemic administration of steroids, and the third had unilateral blindness. Restrictive ventilatory defects were severe enough in five patients to warrant disability and medical discharge from the Air Force.

Some unusual features of the disease such as epididymitis and renal insufficiency are reviewed in detail.

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Tuberculosis-like Disease Caused by Chromogenic Acid-Fast Bacilli*

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MYCOBACTERIA constitute a large and ubiquitous genus of microorganisms with a single definitive feature: acid fastness. Many are saprophytes. Others are mammalian, bird or reptile pathogens. Two species, Mycobacterium tuberculosis and Mycobacterium leprae, have long been known to be responsible for human disease. Most other species have been regarded in the clinical laboratory as saprophytes or contaminants.

In 1953 Buhler and Pollak [*1*] reported two cases of human disease clinically resembling tuberculosis, due to an acid-fast bacillus distinctly different from M. tuberculosis. A distinctive characteristic of these organisms was the development of yellow pigmentation in culture and hence the organism was dubbed the "yellow bacillus." Since that report "atypical" tubercle bacilli have been reported with increasing frequency as disease producers in man.

In the course of studying 559 patients admitted to the Tuberculosis Section of the 2349th U.S.A.F. Hospital between November 1, 1955, and December 31, 1957, atypical acid-fast organisms were isolated on one or more occasions from eleven patients. In six cases it is believed that the atypical organism might represent a secondary invader, or a saprophyte. In five cases it was considered that the evidence was strongly suggestive if not conclusive that these organisms were the causative agent. These five cases are the subject of this report.

CASE REPORTS

CASE I. In January 1956, four weeks prior to hospitalization, a non-tender, firm swelling in the left side of the neck had developed in a five year old white boy. He was living with a grandparent who was said to have inactive tuberculosis. Physical examination revealed no abnormalities except for a hard mass, 3 by 4 cm., in the left submaxillary area, with some superficial fluctuance. He was afebrile.

Complete blood count and urinalysis were within normal limits. Intermediate P.P.D. (0.0001 mg.) skin test gave a 2-plus reaction. Chest roentgenogram revealed moderate bilateral hilar adenopathy with clear parenchyma. Skeletal roentgenograms were normal. Five gastric specimens were negative on culture for acid-fast bacilli.

The clinical diagnosis was tuberculosis of the lymph nodes. Therapy was begun on January 27, 1956, with isoniazed (INH®) 50 mg. twice daily and paraaminosalicylic acid (PAS) 2 gm. three times daily. He was hospitalized on February 2, and on the following day diagnostic lymphadenectomy was performed. The lymph nodes showed one large lymph node, 2 by 3 cm., with tubercles and caseation necrosis, Langhans giant cells, and acid-fast bacteria. (Fig. 1.) There were two smaller nodes which on microscopic section showed only reactive hyperplasia. Stains and cultures were negative for fungi. Culture grew an atypical acid-fast bacillis. (Table I.) Antituberculous chemotherapy was continued for one year.

There was an uneventful recovery and as of March 1957 the patient was doing well.

CASE II. This forty-one year old white man entered Parks Air Force Base Hospital on January 28, 1957, because of pleural effusion. He had had recurring twinges of sharp pain in the left infraclavicular region for three months. This became pleuritic in nature on January 7, 1957. X-ray examination on January 14 showed a left pleural effusion. He has been known to have a heart murmur for ten years, and he did have rheumatism as a child.

There was splinting of the lower left side of the chest, and dullness and diminished breath sounds at the left base. He had a grade 3 aortic systolic murmur

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TABLE I

LABORATORY CHARACTERISTICS OF THE FIVE STRAINS OF ATYPICAL ACID-FAST BACILLI ISOLATED IN THE CASES REPORTED COMPARED WITH M. TUBERCULOSIS

Case No.	Growth Characteristics	Egg Media		Thioglycollate	Catalase	Neutral Red	Sensitivity*			Guinea Pig	Mouse
		27°	37°				SM	PAS	INH		
I	Found only on surgical specimens, yellow to orange, long and large acid-fast bacilli	+	+	+	2+	-	R	MR	R	I plus o.t., no pathology	+
II	Beaded acid-fast rods found only on two surgical specimens, buff to yellow, smooth, weakly cording	+	+	-	4+	-	R	MR	MR	-	+
III	Dried, piled acid-fast bacilli, yellow to orange, photochromogen growth from surgical specimens and sputum	+	+	+	4+	-	R	R	MR	-	+
IV	Photochromogen-buff to yellow, raised smooth and rough colonies, large acid-fast rods beaded	+	+	-	-	-	S	MR	MR	-	+
V	Yellow to orange, weakly cording large beaded acid-fast rods	+	+	+	3+	-	R	MR	MR	-	-
M. tuberculosis	Buff, smooth and rough colonies, slender, solid acid-fast rod, definite cording	-	+	-	2+	2+	S	S	S	+	+
INH resistant M. tuberculosis	Essentially same as INH sensitive M. tuberculosis	-	+	-	-	2+	S	S	R	-	+

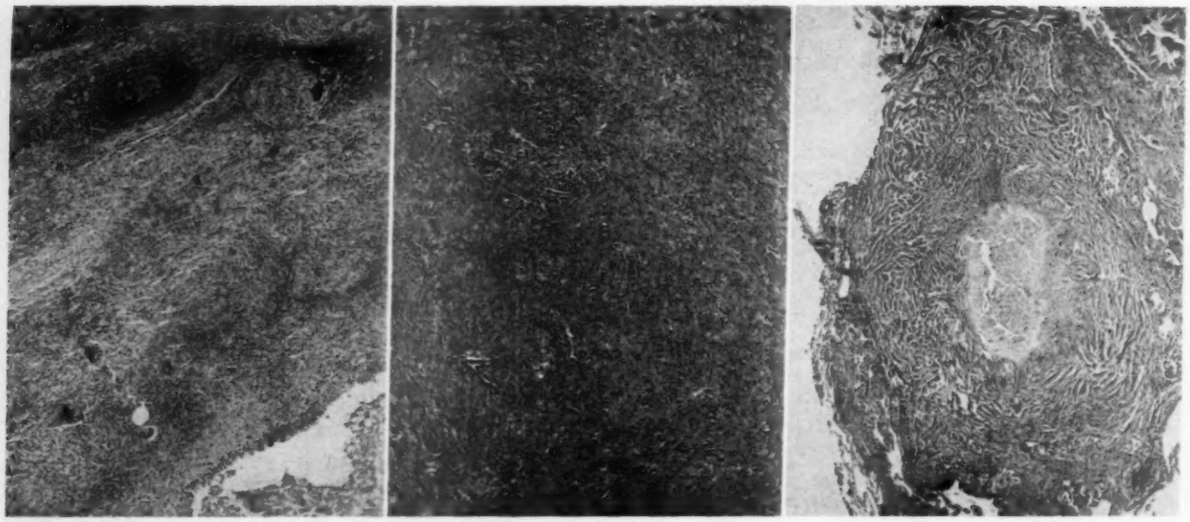
*SM = streptomycin.
S = sensitive.
MR = moderately resistant (growth in 10 mcg./ml., SM, PAS:1 to 10 mcg./ml. INH).
R = resistant (growth in 100 mcg./ml., SM, PAS:25 mcg./ml. INH).

with thrill transmitted up the carotids. A_2 was distant, but audible. There were no other abnormalities.

A P.P.D. intermediate (0.0001 mg.) skin test was 1-plus. Histoplasmin and coccidicidin skin tests were negative. Repeated sputum specimens were negative for acid-fast bacilli by concentrated smear and by culture throughout his course. Gastric cultures revealed no abnormalities. Repeated antistreptolysin titers and C-reactive proteins were within normal limits. Initial roentgenograms showed effusion and slight pleural thickening at the left base.

The patient was asymptomatic and afebrile. Thoracentesis was performed on January 30 and yielded 50 cc. of orange colored fluid, with 11,000 white cells, 76 per cent of which were eosinophils. Pleural biopsy with the patient under local anesthesia on February 3, 1957, showed fibrous tissue without inflammatory changes. Pleural biopsy on March 11 showed fibrous thickening throughout with collections of round cells, fibroblastic activity and no granulomas. (Fig. 2.) The pathological diagnosis was chronic productive pleuritis. Both biopsy specimens produced an atypical acid-fast organism on culture. (Table I.) From March 20, 1957, to April 1, 1958, the patient received streptomycin 1 gm. twice a week, and INH 300 mg. daily. He also received oral penicillin prophylactically. The effusion at the left base cleared slowly as seen on x-ray examination, with reappearance of the left costophrenic angle. There was never evidence of parenchymal disease. On January 19, 1958, he was returned to duty.

The patient's thirty-six year old wife was known to



1 2 3

FIG. 1. Case I. Section of cervical lymph node showing giant cell granuloma with caseation, indistinguishable from tuberculosis.

FIG. 2. Case II. Section of pleural biopsy performed on March 11, 1957, showing non-specific inflammatory changes. Although no granulomatous changes can be found, this specimen and a previous pleural biopsy specimen produced atypical acid-fast organisms on culture.

FIG. 3. Case III. Section of surgical specimen showing granuloma with central caseation. Chromogenic acid-fast bacilli were grown from the specimen.

have a positive reaction to tuberculin tests. In three children, five months through nine years of age, results of second strength P.P.D. tests were negative.

Comment: This is a case of pleural effusion with atypical acid-fast organisms cultured from pleural biopsy on two occasions. M. tuberculosis was never isolated. Granulomas were not demonstrated in the pleural specimen. However, failure to demonstrate granulomas in a pleural biopsy does not rule out tuberculous disease [*2*].

CASE III. This twenty-two year old white man was admitted to this hospital November 13, 1956. In August 1956 he had been admitted to an Air Force Hospital in Utah with complaint of chronic cough of one and a half years' duration. Chest roentgenogram showed a cavity in the right mid-lung field. Histoplasmin skin test was positive, and second strength P.P.D. and coccidioidin tests were negative. Cultures for fungi and tubercle bacilli were negative. The patient was a native of Chicago, Illinois, but had been stationed in Mississippi, Texas, Minnesota and Utah since entry to the service in June 1953. He had contact with a fellow college student in 1953 who was later found to have active tuberculosis.

Temperature on admission was 99.4°F. There were a few small cervical nodes papable, and breath sounds were roughened in the upper right side of the chest posteriorly. The white blood count was 12,300 per cu. mm. with 82 per cent neutrophils, and the erythrocyte sedimentation rate was 3 mm. in one hour. Tuberculin skin tests, repeated on several occasions with second strength P.P.D. (.005 mg.) and old tuberculin 1:100 (1 mg.), were negative. Coccidioidin skin test 1:10 was negative on one occasion and 1-plus on another; histoplasmin was 2-plus, and blastomycin negative.

Numerous sputum specimens were negative on culture for fungi and acid-fast bacilli, except for one specimen on November 19, 1956, which grew out a chromogenic acid-fast organism. This was initially regarded as a contaminant.

Roentgenograms, including planigrams, showed a cavity, 1.5 by 2.5 cm., in the superior segment of the right lower lobe, with no significant change from month to month.

Serial serologic studies for fungi were obtained. Titer was positive to Histoplasma capsulatum yeast phase antigen at 1:16 dilution on August 14, 1956, and remained at that level until February 21, 1957, when the titer was 1:8. It thereafter remained stable. Histoplasmin serology on August 14, 1956, was negative. On November 26, 1956 the histoplasmin titer was 1:256, on December 27 1:128, and remained at that level till April 8, when the titer was 1:64. Serologic studies for coccidioidomycosis and blastomycosis were negative.*

* Performed by the Department of Mycology, Walter Reed Army Hospital.

It was believed that the serologic findings were consistent with a diagnosis of histoplasmosis. Because of persistent cavity and inability to establish a definite diagnosis excision was recommended. Oral amphotercin-B (Fungizone® Squibb) was administered beginning April 4, 1957, and on April 17 the superior segment of the right lower lobe was resected.

On gross examination the specimen showed a cavity, 4 by 2 cm., and several caseous satellite nodules. Histologic examination showed epithelioid tubercles with caseation, Langhans' type giant cells. Acid-fast bacilli were present. Sections stained with Gomori's stain revealed no fungi. (Fig. 3.) Cultures for fungi revealed no organisms. The chromogenic acid-fast bacillis was cultured from the surgical specimen. (Table 1.)

The postoperative course was uncomplicated. Repeat tuberculin skin tests with old tuberculin 1:10 (10 mg.) was negative one month postoperatively. Therapy with streptomycin 1 gm. daily, PAS 12 gm. daily and isoniazed 300 mg. daily was started on May 9, 1957. The patient was transferred to a Veteran's Hospital July 16, 1957.

In two family contacts, age twenty-one and one year respectively, results of tuberculin test with old tuberculin (1 mg.) were negative.

Comment: In this case there is circumstantial evidence for histoplasmosis. The chromogenic organism was cultured from both the sputum and the surgical specimen. Diligent search failed to reveal fungi. It is conceivable that this is an instance of disease due to an organism of low pathogenicity implanting itself on previously diseased tissue. Another point of interest is the repeatedly negative tuberculin skin test.

Case IV. This forty-two year old white man was admitted November 18, 1956, with the diagnosis of moderately advanced pulmonary tuberculosis.

Three days before admission fever, chills and malaise developed. Acid-fast bacilli were found on sputum smear. Roentgenogram showed a soft infiltration in the left apex. During the last year he had had increasingly easy fatigability and mild shortness of breath. There had been 25 pounds of weight loss. In Jaunuary 1956 he had an episode of blood streaking of his sputum. In 1955 he had contact with a man in whom tuberculosis had subsequently developed.

The patient appeared chronically ill, and had dullness, posttussive rales, and a friction rub in the left upper lung field. He was febrile with temperature up to 100°F.

Histoplasmin and coccidioidin skin tests were negative. First strength P.P.D. (0.00002 mg.) skin test was 1-plus. Chest roentgenogram on November 19, 1956, showed extensive patchy soft infiltrate in the left upper lobe and superior segment of the left lower lobe, compatible with moderately advanced tuberculosis. (Fig. 4A.)

Treatment with streptomycin 1 gm. daily, sodium PAS 5.5 gm. three times a day, and INH 100 mg. three times a day was instituted on November 30, 1956, and the patient thereafter became afebrile. By December 18, 1956, there was some clearing of the infiltration, revealing a cavity, 2.5 cm., in the left upper lobe. On March 26, 1957, planigrams revealed the persistence of the cavity. Roentgenograms showed progressive clearing until April 1957. Repeated sputum specimens at monthly intervals cultured out a photochromogenic acid-fast bacilli. (Table 1.) On June 10, 1957, because of the persistent cavity and positive sputum, after seven months of therapy with antituberculous drugs, a left upper lobectomy was performed. Postoperatively, the patient had a paralysis of the left hemidiaphragm.

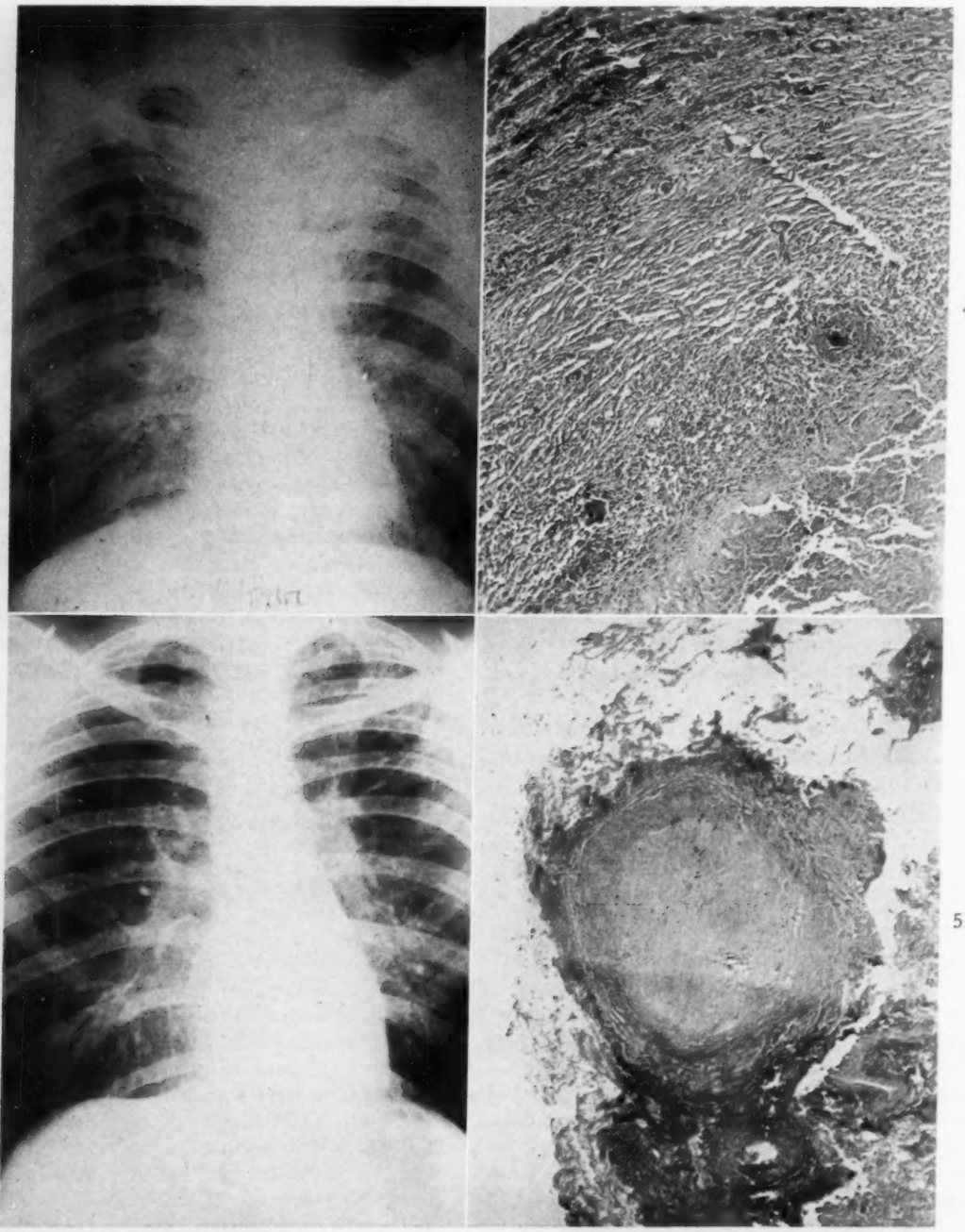
Gross examination of the resected specimen revealed a cavity, 2 cm., in the posterior segment with caseation present. Histological examination showed typical tubercles, Langhans' giant cells, epithelioid cells and acid-fast bacteria. No fungi were seen on Gomori-stained sections, and none grew out on culture. (Fig. 4B.) A photochromogenic acid-fast bacillus identical to that cultured from the sputum was cultured from the surgical specimen.

Of six family contacts, three were negative to old tuberculin 1 mg. and 3 were positive at the time the patient was admitted. Two converted within three months. The other remained negative. No family contact had evidence of disease.

Case V. This twenty-five year old white man was admitted February 11, 1957, because of suspected pulmonary tuberculosis. In October 1953 he was examined for chest pain and chronic sputum production. Roentgenograms at that time showed disease in the area of the first and second left anterior interspace. Sputum cultures were said to have been negative. In January 1957 on re-enlistment examination there was thought to be some spread of the infiltration in the left upper lobe. On entrance to the service in 1951 a minifilm was within normal limits, but in retrospect, disease was present in the left first anterior interspace. There were dry rales heard posteriorly over the left upper lobe on admission physical examination.

Skin test with old tuberculin 1:100 (1 mg.) was initially equivocal but on repeat was 1-plus. Histoplasmin and Coccidioidin skin tests were negative. Mycobacterium tuberculosis was never cultured. Sputum on concentrated smear was positive for acid-fast bacilli in March, April and May 1957. Sputum specimens in March and April 1957 grew an atypical acid-fast organism. (Table 1.)

The patient was asymptomatic and afebrile. Chest roentgenogram taken on admission showed an infiltrative process in the left upper lobe with areas of cystic change or cavitation. (Fig. 5A.) Therapy was started



4A 4B

5A 5B

FIG. 4. Case IV. A, chest roentgenogram, November 10, 1956, showing disease in the left upper lobe. Planigrams showed cavitation. B, specimen showing caseous granuloma. Acid-fast bacilli were seen on tissue sections, and atypical acid-fast organisms were cultured.

FIG. 5. Case V. A, chest roentgenogram, February 1957, showing infiltrate in the left upper lobe. Cavitation was demonstrated by planigram which persisted after seven months of therapy. B, section of surgical specimen showing caseous granuloma.

on January 19, 1957, with streptomycin 1 gm. twice a week and INH 100 mg. three times a day. Planigrams in February 1957 showed a cavity. Planigrams September 25, 1957, showed a persistent cavity, and a left upper lobectomy was performed December 2, 1957. Gross specimen removed from the left upper lobe at surgery showed no cavitation. There were gross nodules which on sectioning showed caseation. Histological examination showed numerous caseating epithelioid tubercles, surrounded by moderate

amounts of fibrotic reaction. There were scattered Langhans' giant cells. Some tubercles showed calcification. Acid-fast bacilli were present. (Fig. 5B.) Culture of the surgical specimen grew the atypical acid-fast organism. (Table 1.) Fungus stains and cultures were negative. He had an uneventful recovery, except for persistence of a small air pocket for four months. He returned to duty on May 30, 1958.

In his wife, age twenty-three, results were negative to old tuberculin 1 mg.

Comment: Cases IV and V illustrate disease clinically and radiologically indistinguishable from pulmonary tuberculosis. Tuberculin skin tests were positive. M. tuberculosis was never isolated. However, atypical tubercle bacilli were isolated from the sputum on multiple occasions, and from the surgical specimen after seven and ten and a half months of drug therapy respectively.

COMMENTS

Identification of the tubercle bacillus, and proof of pathogenicity has in the past rested on the growth and cultural characteristics, acid fastness, and production of disease in guinea pigs. These criteria are no longer adequate, and numerous aspects of morphology, biochemical reactions, drug sensitivity and animal pathogenicity are being investigated in an effort to further define the members of the mycobacteria genus and to distinguish M. tuberculosis from saprophytic and from other pathogenic acid-fast bacteria.

Various properties of the organisms isolated in the group of cases presented are tabulated (Table 1) and compared with M. tuberculosis.

Growth Characteristics and Morphology. M. tuberculosis grows on a number of media, solid and liquid. We have routinely used modified Petragnani's egg medium, incubated at 37°C. M. tuberculosis grows readily in a minimum of three weeks appearing as a buff, smooth or rough colony. M. tuberculosis does not grow on Sabouraud's medium or thioglycollate broth, nor will it grow at 27°C, even on egg rich media. In contrast all of the "atypical" organisms isolated from these cases grew at room temperature on egg media, and three strains grew readily in thioglycollate broth. Yellow pigmentation was a characteristic of all strains. In general the atypical mycobacteria are longer, broader, show more prominent beading than do tubercle bacilli. In addition, M. tuberculosis tends to grow in parallel orientation ("cording"); this tendency is much less marked or absent in the chromogens.

Biochemical Tests. The neutral red test [*3*], was used as a measure of pathogenicity of acid-fast organisms. Pathogenic M. tuberculosis readily fix the dye in the presence of alkaline buffered solution. Reference to Table 1 shows that in none of the chromogens recovered from these patients were there positive results from neutral red tests.

The catalase test [*4*] is a rough measure of catalase activity, using 30 per cent hydrogen peroxide as an indicator. The degree of bubblings produced is graded from 0 to 4-plus. M. tuberculosis usually produces a 2- to 3-plus reaction, although isoniazid resistance has been shown by Middlebrook to be associated with loss of catalase activity. Saprophytic acid-fast bacilli show greater catalase activity. The pathogenic chromogens generally show increased catalase activity, in spite of moderate to marked resistance to isoniazid. (Table 1.)

Most strains of M. tuberculosis, initially isolated from previously untreated patients, are susceptible to streptomycin, para-aminosalicylic acid, and isoniazid. In recent years occasional instances of drug resistance are encountered without previous known exposure to drugs. However, in over 500 "original treatment" cases of tuberculosis seen at this hospital, no cases of initial drug resistance have been encountered.

All the chromogenic organisms isolated showed moderate to marked resistance to two or more of the three major antituberculosis drugs.

The guinea pig has traditionally been the test animal utilized in establishing the pathogenicity of acid-fast organisms; M. tuberculosis also regularly produces disease in mice. Isoniazed resistant strains tend to lose their pathogenicity for guinea pigs. None of this group of chromogens produced disease in guinea pigs, although in one animal (Case 1) weekly tuberculin skin tests revealed positive results. All but one strain (Case V) produced disease in the mouse.

Chromogens. Photochromogenic organisms are those which develop a pigment only when allowed to grow after exposure to light. When suspected, two culture tubes ought to be inoculated, and one wrapped so as to exclude light. When the unwrapped tube develops a color, it may be compared to the wrapped tube. After exposure to light the wrapped tube will then develop a color even if grown in the dark. Scotochromogens develop color in the dark.

A definitive classification of atypical mycobacteria causing tuberculosis-like disease cannot

be given. However, Runyon [*5*], on the basis of many cultures submitted from all over the country, proposed a classification: (1) photochromogens, (2) scotochromogens, (3) a heterogenous group which is undoubtedly many subgroups. The photochromogens are the most prominent in disease production and account for many other reports of atypical organisms dating back to the 1930's.

In order to classify finally this diverse group of organisms, further research is necessary. This research must encompass the clinical course, pathological findings and bacteriologic investigation of all cases of disease in which nontuberculous acid-fast organisms are found. Unusual organisms ought not to be discarded but intensively studied until such time as a working classification can be achieved.

CLINICAL ASPECTS

Atypical (chromogenic) acid-fast organisms have been found associated with a wide variety of clinical syndromes, which have a disease spectrum similar to that of human tuberculosis. Buhler and Pollack [*1*] and Wood et al. [*6*] in 1953 reported on a series of sixteen cases of disease due to the "yellow bacillus," a photochromogenic mycobacteria. Fourteen of those patients had pulmonary involvement, and six had involvement of other systems (lymph nodes, genitourinary system, peritoneum and cerebrospinal fluid).

A number of cases of bone and lymph node disease from which only "saprophytic" acid-fast organisms were recovered, was recently reported from the Mayo Clinic [*7*]. Prissick and Masson reported a similar group of cases including ten of cervical adenitis in children, associated with nontuberculous acid-fast bacteria [*8*]. Wolinsky et al. reported three cases of pulmonary disease, two associated with photochromogens, and one with a scotochromogen [*9*].

The actual clinical course of infections due to photochromogens and other atypical acid-fast organisms has not been well defined because of the relative paucity of cases and lack of controlled study. At our hospital there were five such cases out of 559 admissions to the tuberculosis section. An additional six patients had atypical organisms as well as M. tuberculosis. Crow et al. [*10*] noted that one out of 100 admissions to a large tuberculosis hospital consistently had atypical organisms.

These last authors also noted that there were fewer reactors to tuberculin among the family contacts of their patients than would have been expected among contacts of a similar group of patients with M. tuberculosis, suggesting the disease to be possibly less contagious [*10*].

The disease caused by atypical organisms seems to be rather indolent in progression, and to have rather milder symptoms than tuberculosis of similar extent [*6,10*]. Also there seems to be a poorer response to drug therapy, as manifested by slowness of conversion and cavity closure [*9*]. This latter situation is probably a reflection of the varying degrees of resistance to one or more drugs noted in most studies [*5,6,8–10*]. Those patients with widely disseminated disease seem to do especially poorly [*6*].

In the five present cases, and in the other series mentioned previously, the pathological specimens that were studied were indistinguishable from similar clinical disease caused by M. tuberculosis. On gross examination tubercles with caseation are found. On tissue section there is a granulomatous response with epithelioid tissue, giant cells and caseation. Acid-fast organisms may be seen in the tissues.

The diagnosis of disease caused by "atypical" acid-fast organisms is difficult. The clinical course and roentgenographic appearance and pathology of the disease mimics that of M. tuberculosis. It is only by careful attention to the organisms which are recovered from the patient that the nature of the process can be ascertained. Simple smears are inadequate in the diagnosis of tuberculosis and of disease caused by atypical organisms. When an atypical organism is cultured, it should not quickly be discarded as a contaminant or a saprophyte. Careful and meticulous bacteriologic study must be made to show whether or not a particular organism is a pathogen. Until more is known, cases of tuberculosis-like disease must be isolated and treated as tuberculosis.

SUMMARY AND CONCLUSIONS

1. Five additional cases of tuberculosis-like disease from which only non-tuberculous acid-fast bacilli were isolated are presented.

2. Disease associated with non-tuberculous or "atypical" mycobacteria is being reported more and more frequently in recent years, presumably because more routine cultures are obtained and there is greater alertness on the part of the physician.

3. The disease produced by "atypical" organ-

isms is entirely similar clinically and pathologically to disease caused by M. tuberculosis.

4. All unusual organisms isolated from suspect cases of tuberculosis should be carefully studied so that when sufficient cases have been recorded, a practicable classification for diagnosis and treatment may be evolved.

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Mechanics of Respiration in Bronchial Asthma*

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THE difficulty in evaluating the actual degree of disability of patients in various stages of bronchial asthma is well known to the pulmonary physiologist and clinician alike. The relatively recent development of procedures capable of measuring the pulmonary airflow resistance as well as the elastic properties of the lung provide more quantitative and reliable methods of evaluating this common clinical entity [*1,2*]. An accurate numerical expression of airflow resistance in patients with bronchospasm of whatever cause is important in any attempt to define factors in the origin or therapy of this condition.

During spontaneous breathing the muscular act of inspiration is opposed by two major forces: (1) the force of elastic resistance which is dependent upon the change in volume or degree of inflation of the lungs; and (2) the force of nonelastic resistance which is made up of the force of viscous resistance and the resistance to airflow through the tracheobronchial tree. This second force is dependent upon the rate of change of volume or velocity of airflow. The elastic property of the lung, termed compliance, is expressed as the volume change in L./cm. H_2O pressure difference between the pleural surface and the mouth. Pulmonary flow resistance which includes tissue viscous resistance is expressed in cm. H_2O pressure differential per liter per second.

This report presents observations on the mechanics of respiration in ten patients with long standing bronchial asthma during periods of acute respiratory distress and following relief or improvement of symptoms as a result of therapy. Brief clinical protocols of the ten patients are presented in the appendix.

METHODS AND MATERIALS

All subjects were studied during spontaneous breathing while in the sitting position no earlier than two hours after their last meal. The pressure volume characteristics of the lungs were determined by the method of Mead and Whittenberger [*3*]. The intraesophageal pressure was obtained by using a 75 cm. long, 1.4 mm. internal diameter polyethylene tube with multiple perforations at its terminal end that were enclosed in a thin latex balloon 15 cm. in length and approximately 5 ml. in capacity [*4*]. The balloon and catheter were moistened with cold water and passed with ease via the nares into the lower third of the esophagus. The catheter was connected to a Sanborn differential pressure transducer (type 467 B) which recorded the pressure difference between the esophagus and mouthpiece. Tidal volumes were obtained using a special 9 L. Collins Spirometer‡ with 1½ inch diameter tubing and low resistance valves. Volume tracings were obtained by the use of a rotational potientiometer attached to the spirometer wheel. The output of the potientiometer which was proportional to the rotation of the wheel was led into a direct writing oscillograph where it was recorded simultaneously with pressure. Before recording, the esophageal balloon was evacuated, and then filled with 1 ml. of air. The exact length of the catheter from nares to terminal end was recorded in order that subsequent procedures on the same patient be carried out at the same catheter position.

Pulmonary compliance was recorded as the ratio of volume to change in pressure occurring between the beginning and end of inspiration (points of zero flow) and was expressed in L./cm. H_2O. The average total pulmonary flow resistance was recorded as the ratio of the total pressure change to the corresponding change in the rate of airflow between points of equal lung volume in inspiration and expiration [*5*]. The measurement of flow resistance for inspiration or expiration separately was calculated as the ratio of the difference between the change in transpulmonary pressure due to the elastic component of pressure and the total change in pressure between the point of onset of inspiration (or expiration) and a point at mid-inspiration (or expiration) to the volume flow per unit time occurring

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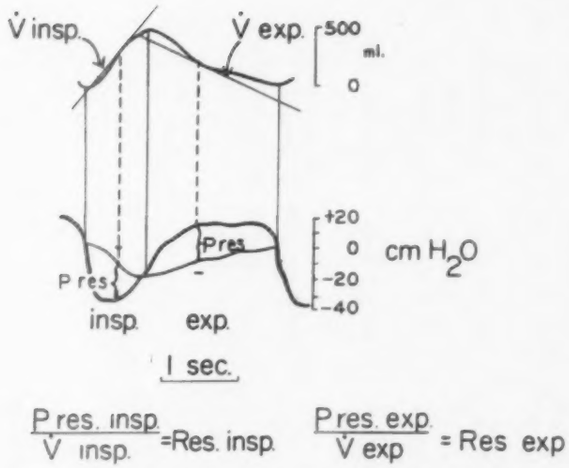


FIG. 1. Method of calculating inspiratory and expiratory flow resistance separately. Vertical solid lines originate from points of zero air flow. Vertical dashed lines originate from points of maximum flow.

at the two points. (Fig. 1.) The elastic component was derived from the measurements of compliance and volume change that had occurred between the two points [*6*].

Work of breathing was calculated from pressure-volume loops plotted from the simultaneous pressure-volume recordings of three to six representative breaths. By planimetric integration of these loops an approximation of average work done on the lungs could be determined. Since the work of breathing in these patients involved active work during expiration, integration of these loops included the area circumscribed by the expiratory pressure-volume tracing beyond the resting end expiratory pressure as well as the area under the curves produced by elastic and inspiratory flow resistive work. Figure 2 describes the work loop of one of the subjects with very high flow resistance. The width or "fatness" of this loop is compared to that of a normal subject. Work was also estimated from the formula 0.79 PV̇ where P equals the total transpulmonary pressure change during a full respiratory cycle expressed in cm. H_2O and V̇ the minute ventilation in liters. This formula derived by McIlroy et al. [*2,5*] treats the pressure-volume loops as an elipse and is approximately correct when the work is principally flow-resistive. Since it appeared that practically all the respiratory work being done in these asthmatic subjects was flow resistive rather than elastic work, this formula was employed.

Each recording included tracings of twelve to fifteen breaths, at least ten of which were analyzed to obtain the average values of airflow resistance and compliance. Respiratory rate, tidal volume, resting end expiratory pressure, maximal inspiratory capacity, and vital capacity were recorded with each run. In most subjects it was possible to obtain the maximal static inspiratory pressure that could be developed.

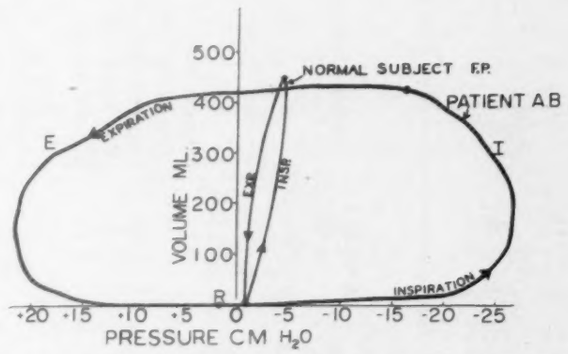


FIG. 2. Comparison of pressure-volume loops of patient A. B. and normal subject F. P. Work of breathing for patient A. B. is area inside larger loop R I E R. Point R represents the resting end expiratory pressure of patient A. B.

This was measured at the end of the inspiratory capacity effort with the glottis open and at zero airflow. All gas volumes were recorded at ATPS (73°F. ± 2°). Before and after each run calibrations of pressure were made with a water manometer, and volume calibrations with a water volume displacement system of a standard pneumothorax apparatus.

When a bronchodilator was administered, isoproterenol HCl, U.S.P., was used in nebulized form during the course of five slow deep inspirations for a total dose of .30 to .45 mg. per patient. Aminophyllin when used was given intravenously or in solution per rectum in doses of 250 to 500 mg. (Table I.) Four of the ten patients failed to demonstrate any significant change in airway resistance as the result of therapy at the time of their first study. Repeat studies were carried out when optimum improvement was noted clinically. The time interval between each study is noted in Table I.

RESULTS

The data from the individual studies before and after therapy of each of the ten patients are presented in Table I. All ten patients as noted in the appendix had had many attacks of asthma in the past, had been seen by numerous members of the Chest and Allergy Clinics, and were classified by all as having chronic bronchial asthma. One patient (E. L.) also had chronic pulmonary emphysema and arteriosclerotic heart disease as is noted in the clinical summary presented in the appendix.

Patients I to V were observed during periods of marked distress either during an attack of bronchial asthma or immediately following. The values of mean airway resistance in these five patients ranged from 25.0 to 56.5 cm. H_2O/L./second. At the time of the study they demonstrated labored wheezing respirations which had

TABLE I

RESULTS OF STUDIES BEFORE AND AFTER THERAPY

Case No.	Patient	Age (yr.)	Height (cm.)	Weight (kg.)	Respiratory Rate (per min.)	Tidal Volume* (ml.)	Mean Airway Resistance (cm./L./sec.)	Compliance (L./cm.)	Resting End Expiratory Pressure (cm. H_2O)	Maximum Inspiratory Pressure (cm. H_2O)	Inspiratory Capacity* (L.)	Vital Capacity* (L.)	Work of Breathing† (kg.M./min.)	Comments‡
					(15)	(500)	(1.5–3.0)	(.15–.30)	(−2 to −6)	(−25 to −35)			(.15–.20)	
I	A. B.	54	180	86.0	b§ 20	450	53.4	.028	+2	....	....	....	3.59	Isoproterenol
					a‖ 20	745	14.1	.027	−4.4	....	1.9	2.2	....	Fog Room 2 hr.
II	P. G.	41	160	75.5	b 18	250	56.51	.016	−7	....	....	....	1.08	Isoproterenol
					a 20	550	17.8	.041	−4	−28	1.39	1.62	....	Fog Room 2 hr.
III	K. Y.	51	157.5	88.0	b 24	340	55.1	.017	+8	−20	.64	.64	3.95	Isoproterenol
					a 22	680	13.1	.041	−4	....	1.4	1.75	....	1½ hr.
IV	M. G.	53	165	56.5	b 16	295	41.5	.021	−6	−36	.55	.75	1.31	Prednisone
					a 16	520	3.69	.133	−3.5	−16	1.76	2.30	....	10 wk.
V	M. C.	40	150	52.5	b 21	480	25.0	.036	−3	....	1.2	1.2	2.06	Prednisone
					a 17	630	3.63	.154	−3	−20	1.84	2.56	....	4 wk.
VI	J. T.	37	172.5	72.5	b 22	600	17.9	.064	−7	−29	1.2	1.8	2.24	Prednisone
					a 17	1000	5.83	.187	−5	−20	2.7	4.1	....	14 wk.
VII	C. C.	65	164	62.5	b 21	440	24.7	....	−6.3	....	.60	.60	2.21	Isoproterenol
					a 18	840	15.3	.079	−4	....	.97	.97	....	50 min.
VIII	R. L.	51	164	68.5	b 20	490	22.0	.089	−5	−34	.70	.70	2.08	Aminophyllin
					a 16	775	42.4	.219	−3	−16	1.83	2.4	....	9 mo.
IX	R. K.	63	169.5	59.0	b 20	400	17.3	.067	−6	−26	1.35	1.40	.94	Isoproterenol
					a 24	605	12.5	.100	−6	−28	1.8	1.8	....	10 min.
X	E. L.	52	175	91.4	b 22	330	22.4	.151	−4	− 6	1.6	2.0	1.29	Isoproterenol
					a 26	450	12.3	.163	−3	− 6	1.4	2.0	....	10 min.

NOTE: Figures in parentheses represent normal values.

* BTPS.

† Derived from integration of work loops.

‡ Major therapy or medication in use during period of improvement with time interval between studies before and after.

§ b = before therapy.

‖ a = after therapy.

TABLE II

INSPIRATORY AND EXPIRATORY AIRWAY RESISTANCE BEFORE AND AFTER THERAPY

(All values in cm./L./sec.)

Case No.	Patients	Inspiratory			Expiratory			Expiratory/Inspiratory	
		Before Therapy	After Therapy	% change	Before Therapy	After Therapy	% Change	Before Therapy	After Therapy
I	A. B.	36.97	8.85	76.0	93.13	22.19	76.1	2.52	2.50
II	P. G.	45.0	12.38	72.5	64.71	22.5	65.2	1.43	1.82
III	K. Y.	39.0	8.76	77.5	83.2	28.53	65.7	2.13	3.26
IV	M. G.	45.0	4.26	90.5	50.9	5.3	89.6	1.13	1.24
V	M. C.	26.2	3.34	87.3	31.2	4.74	84.8	1.19	1.42
VI	J. T.	11.4	5.1	55.3	32.7	7.6	76.7	2.86	1.49
VII	C. C.	18.3	10.2	44.5	41.0	33.0	19.5	2.24	3.23
VIII	R. L.	14.4	3.6	75.0	54.0	6.5	87.9	3.75	1.83
IX	R. K.	14.16	8.14	42.5	21.71	19.2	11.5	1.52	2.36
X	E. L.	24.3	11.4	53.1	22.4	14.2	36.6	.92	1.24

Case No.	Normal Subjects	Inspiratory	Expiratory	Expiratory/Inspiratory
I	F. P.	2.13	3.07	1.44
II	F. G.	1.76	3.41	1.93
III	J. B.	3.39	4.5	1.32
IV	R. W.	2.27	3.46	1.52
V	D. J.	1.23	1.93	1.56

responded poorly to maximal therapy. Patients VI to X had mean airway resistance values ranging from 17.3 cm./L./second to 24.7 cm./L./second and also were in chronic respiratory distress but of slightly less severe form. A previously studied group of ten normal adults in this laboratory had a range of values for total (inspiratory plus expiratory) airflow resistance of 1.40 to 3.97 cm./L./second with an average of 2.41 $\pm$ 0.7 cm./L./second. Table II presents values for separate inspiratory and expiratory airway resistance as well as the ratios of the expiratory to inspiratory resistance before and after therapy. Studies of this ratio in twenty-eight normal subjects over the age of fifty by Frank et al. [*6*] showed a mean value of 1.6. Similar studies by Attinger and his co-workers [*7*] gave values for this ratio in the range of 1.3 $\pm$ .3. In the ten asthmatic subjects reported here in this expiratory to inspiratory resistance ratio varied considerably from patient to patient (range .92 to 3.75). Following therapy, seven of the patients showed an increase in this ratio while three showed a decrease. There appeared to be no correlation between this ratio and the absolute value of the resistance or the magnitude of its change. Of the total of twenty derived ratios (ten before and after therapy) only five fell within the normal range; eleven were higher and four lower. Patient E. L. had a negligibly higher inspiratory than expiratory resistance before therapy; all other ratios of expiratory to inspiratory resistance were always greater than 1. Six of the patients showed a greater relative change in their inspiratory flow resistance after therapy than was shown in their expiratory resistance. Two showed the same degree of change and two showed a greater change in the expiratory resistance following therapy.

The work of breathing was elevated in all ten subjects, ranging from 0.94 to 3.95 kg. m./minute or from five to twenty-five times the amount of work done by the normal adult at rest. The values for the normal were derived from the work loops of the five normal subjects. In the asthmatic patient virtually all the extra pulmonary work would appear to be due to the high resistance to pulmonary airflow as none of the

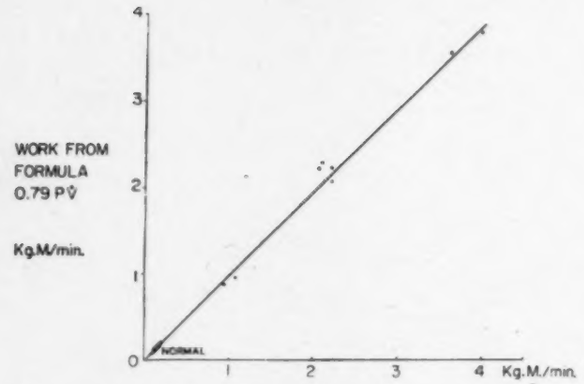


FIG. 3. Work of breathing derived from integration of plotted pressure-volume loops versus work calculated from formula of McIlroy, 0.79 PV̇.

ten subjects had a minute volume before therapy of over 10 L./minute. As will be noted in Figure 3, in which work derived from the pressure-volume loops is compared with the formula for purely viscous work, there would appear to be a satisfactory correlation of these two methods. It is not suggested that these ten points are adequate to describe a curve, however the slope of the line drawn through these few points suggests the formula may permit an adequate approximation of the work of breathing under the conditions described here. It is to be emphasized that these values of pulmonary work apply only to the work done on the lungs, for the elastic characteristics of the thorax are unknown and not measured by these methods. Otis [*8*] has pointed out that these methods underestimate the work done on the lungs for they neglect the interaction between the lung and chest wall.

The values for compliance before and after therapy listed in Table 1 should be compared with the corresponding values for airway resistance. There would appear to be a reciprocal relationship between these two values. The factors related to these changes in compliance before and after therapy will be discussed herein. The value of the compliance before therapy in patient C.C. is missing because the points of zero flow could not be accurately determined. In six patients the maximal inspiratory static pressures were obtained prior to therapy and as noted fell within the normal range in five of these subjects. The one patient whose maximal pressure was well below the normal range (less negative on an absolute scale) was the patient with pulmonary emphysema.

The tidal volume in all ten subjects was higher following reduction in the elevated mean airway resistance. With the negligible changes in the respiratory rates the resulting minute volumes were higher following therapy in all ten cases.

COMMENTS

Airway Resistance. Bronchial asthma has been described as a syndrome of many causes in which episodes of labored wheezing respirations occur between periods of apparent normal respiratory behavior. There are few if any conditions other than foreign body aspiration that produce such maximal respiratory efforts as attacks of severe bronchial asthma. It would appear that most of the energy in this effort is devoted to overcoming the high resistance to airflow in and out of the bronchial tree. The occasional rapidity of onset of an attack of asthma as well as the sometimes dramatic and rapid relief obtained with parenteral therapy suggest a highly dynamic and rapidly acting system that controls the tone and patency of the bronchial tree. The spirally layered bands of muscles enveloping the tracheobronchial tree are nicely arranged to effect an acute constriction of the bronchi [*9*]. It is not suggested that constriction of these muscular bands represents the sole explanation of acute bronchial obstruction in asthma. It is possible that gradual accumulation of retained bronchial secretions, as may develop during sleep or with respiratory infections, reaches a point of significant encroachment upon the bronchial lumen and precipitates attacks of wheezing and dyspnea. This hypothesis would appear to be supported by the report of many of these asthmatic subjects who note that they are more likely to have an attack in the early morning hours; however if immediately upon awakening they can cough up an adequate volume of (tenacious) mucus, an attack of wheezing and dyspnea will not follow. In a syndrome such as bronchial asthma there are probably many factors involved in the pathogenesis of these attacks, but at present acute bronchoconstriction due to the action of the extrinsic muscular bands or the retention of bronchial secretions or a combination of both would seem to be the most plausible explanations of the origin and rapidity of onset of the majority of acute attacks.

Once an asthmatic attack is initiated there may be other factors responsible for its continuance. Possibly the major one of these is the "check valve" mechanism described by Dayman

[*10*] in a study on patients with emphysema. The essence of this mechanism is that during the forced expiration in patients with emphysema there is greater pressure developed in the parenchyma of the lung tissues and the outside of the airway than there is within the airway thereby causing its narrowing or collapse. During inspiration this pressure gradient is reversed as the intrathoracic pressure on the outside of the airways becomes more negative while that within the bronchi remains atmospheric. There have been various reports [*11–13*] suggesting asthma or induced episodes of bronchoconstriction in normal volunteer subjects produces the hyperinflation or pressure-volume characteristics of the emphysematous state. Laennec [*14*] was the first to describe the increased resistance to flow on expiration and in patients with asthma and emphysema he likened this mechanism to the "valve of an air gun." Neergaard and Wirz [*15*] proved this thesis with actual pressure volume measurements in patients with asthma and emphysema. Measurements of expiratory versus inspiratory airflow resistance in normal subjects has been reported as showing no significant difference by a number of authors [*6,7,13,16*]. From the statements and data presented in these various reports a ratio of expiratory to inspiratory resistance of 1.6 or less was interpreted as not significant. Similar studies [*13,17*] upon patients with bronchial asthma during their asymptomatic intervals revealed this ratio to be within the same range as that of the normal subjects. Of the ten patients reported herein during episodes of respiratory difficulty and with high pulmonary flow resistances five had an expiratory to inspiratory ratio of 2.1 or higher while five had a ratio of 1.5 or less. These ratios show no correlation with the degree of clinical disability or actual total airflow resistance. If one arbitrarily chooses a ratio of 2.0 or more as the dividing line between the presence and absence of a "check valve" mechanism, then only half the patients demonstrated this phenomenon. As already mentioned there are probably many factors involved in the perpetuation of an attack of asthma. The suggestion that one of these factors is the "check valve" mechanism of expiration is probably valid but may not apply in all cases of bronchial asthma.

Compliance. In each instance that the pulmonary flow resistance fell toward normal following therapy there was a corresponding increase in the pulmonary compliance. This reciprocal change may be explained by the findings reported by Otis et al. [*11*] which described factors in the distribution of pulmonary ventilation. This fundamental work demonstrated that a decrease in compliance with increased breathing frequency reflected an altered distribution of ventilation and in such cases the increase in frequency resulted in changes of the over-all volume-elastic and flow-resistive properties of the system. Mead et al. [*16*] noted that partial occlusion of one respiratory pathway, with the opposite pathway remaining open, resulted in the partially obstructed lung participating less in the total volume change as the respiratory rate was increased. The high pulmonary flow resistance noted in the ten patients reported here would have a similar effect upon the elastic properties of the lung by way of reducing the amount of lung being ventilated. Upon reduction of the pulmonary flow resistance a greater volume of lung becomes ventilated with a corresponding increase in compliance.

The unusually low compliance noted in these patients during the episodes of acute respiratory distress suggests that fundamentally very little lung was being ventilated. The extremely high values of flow resistance would also suggest that a major portion of the tracheobronchial tree was markedly constricted which might possibly explain the marked functional loss of lung volume being ventilated. With relief of this obstruction the compliance values rose toward normal in every case.

Another factor contributing to the increase in compliance following therapy may be the change in the mid-position of the lung on the pressure volume curve. Since this curve approaches a plateau at its upper levels [*1*] the value for the slope of this curve (compliance) will increase as the resting mid-position descends on the curve. Hurtado and Kaltreider [*12*] demonstrated this change in the mid-position and the lung volumes following therapy in patients with bronchial asthma. What fraction this latter factor contributed to the total change in compliance was not determined by the methods used in this study.

Maximal Pressures and Minute Volume. As noted earlier maximal intrathoracic pressures that were within the normal range developed in the majority of patients. The finding in one patient (E. L.) whose maximal pressure remained at −6 cm., both during and after an episode of respiratory distress, might be ex-

plained on the basis of his underlying emphysema. Mead et al. [*16*] studied the maximal inspiratory pressures in a group of six patients with emphysema and found in all but one case that the maximal values were never greater (less negative) than −11 cm.

It was also noted in the present study that during the time of the asthmatic attacks the minute volumes never exceeded 10 L./minute. Following therapy with reduction in flow resistances the minute volumes increased in every case. A reduction in minute ventilation as a result of an added increase in resistance to airflow was reported by Cain and Otis [*18*]. They noted increased resistances resulted in increased time required for inspiration and expiration. This time requirement to complete an adequate tidal respiration might explain in part the apparent limitation in minute volume found in these ten asthmatic subjects.

Work of Breathing. As is apparent to anyone observing a patient during an attack of bronchial asthma, all available energy appears to be devoted to getting air in and out of the lungs. Since the minute volume in all ten subjects did not exceed 10 L./minute the marked elevations in the values for pulmonary work must be primarily due to the work done in overcoming the high airway resistance. As pointed out under Results the values for pulmonary work recorded in Table I do not report the total work done, i.e., the work done on the chest wall and the abdomen as well as the lungs. Therefore these marked elevations of work underestimate the actual total respiratory work being done. In an attack of asthma the primary aim of therapy is the relief of dyspnea which can be accomplished by reducing the high energy expenditure devoted to the work of breathing. The greatest therapeutic benefit will derive therefore from procedures designed to reduce the high air flow resistance. Whether this involves nebulized bronchodilators, sedatives, general anesthetics or a host of other treatments and procedures, relaxation and dilatation of the bronchi will lead to less work. When a patient dies as a result of an attack of bronchial asthma, it is apparent that severe fatigue or exhaustion is a major factor contributing to the event. Riley [*19*] in a lucid editorial on the work of breathing emphasizes this aim of therapy in reducing the work of breathing in patients with severe airway obstruction. He points out that an increase in the work of breathing seriously curtails the amount of oxygen available for non-ventilatory work. The oxygen cost of breathing was not determined in the ten subjects studied here but it was clinically apparent there was little energy remaining for non-ventilatory work. There have been no reports describing the oxygen cost of breathing in patients with pulmonary flow resistances in the range of values reported here; however, Cournand et al. [*20*] did determine the oxygen cost in a patient with severe emphysema and high flow resistance before and after therapy. They found that during the period of "considerable obstruction" the oxygen cost of breathing when the minute ventilation was over 5 L./minute was 25 ml. of oxygen/L. ventilation/minute and after relief of the obstruction the oxygen cost was 6 ml./L. ventilation/minute when the minute ventilation exceeded 15 L./minute. It was concluded from this study that dyspnea in such patients was conditioned not only by the reduced maximal breathing capacity, but also by the excessive work required of the respiratory muscles at any level of ventilation and that the work was equivalent to an increase of over 50 L./minute in a normal subject. The principle of the excessive work required of the respiratory muscles seems quite applicable to the situation found in the ten asthmatic subjects in the present study. Using the analogy of the equivalent work that would be required of the normal subject it was calculated that the work of breathing of patients I or III during their asthmatic attack would require a normal subject with normal airflow resistance to ventilate 85 L./minute to equal the same amount of work. If such a derivation is valid, it re-emphasizes the magnitude of the energy expended by these patients during their periods of acute respiratory distress. The various medications and procedures aimed at lowering the airway resistance in the asthmatic subject will therefore have their major effect in reducing the work of breathing; the first and most important step toward eventual recovery.

SUMMARY AND CONCLUSIONS

Observations upon ten patients with chronic bronchial asthma during periods of acute and chronic respiratory distress demonstrate the mean airway resistance to be markedly elevated in all cases. In some instances this resistance is found to be twenty-five times higher than normal.

Analysis of the individual inspiratory and expiratory airway resistances indicates that the

inspiratory airway resistance may be almost as high as the expiratory resistance. Moreover the majority of patients studied here exhibited greater improvement in the inspiratory resistance than in the expiratory resistance following therapy. The prevailing impression that most if not all the obstruction to airflow in bronchial asthma is always in the expiratory phase is not supported by the results obtained here.

The "check valve" mechanism of expiration as described in patients with emphysema is probably operative in many patients with bronchial asthma during their acute attacks. Based on the relatively equal values of expiratory and inspiratory flow resistance found in half the ten patients studied it is possible this mechanism may not always be operative in all cases.

The elastic resistance of the lungs expressed as compliance appears to decrease as non-elastic (airway) resistance increases. This reciprocal relationship within the limits of the method used here is discussed briefly.

The work of breathing in patients during attacks of bronchial asthma is markedly elevated and is due almost entirely to the work done overcoming airway resistance. Any therapeutic procedure directed toward lowering the elevated airway resistance is therefore rational and justified on the physiologic basis of its effectiveness in diminishing the work of breathing.

Acknowledgment: I wish to express my deep gratitude to Drs. Jere Mead and N. R. Frank of the Harvard School of Public Health for their encouragement and advice during the period of study, and specifically to Doctor Frank for his helpful assistance in preparing the various procedures, and to Doctor Mead for his most valuable comments and criticisms of the manuscript. I am also indebted to Dr. John Harter who referred most of the patients for this study and assisted greatly in having them understand the procedure. The technical assistance of Miss V. Rice is gratefully acknowledged.

APPENDIX

CASE REPORTS

CASE I. A. B. was a fifty-four year old man who had had recurrent bronchial asthma for thirty-one years. The original episode of asthma had followed the development of a lung abscess subsequent to tonsillectomy. Subsequent attacks had invaribly followed upper respiratory infections. Examination revealed a blood pressure of 130/80 mm. Hg. During attacks breath sounds were diminished and inspiratory and expiratory wheezes and rhonchi were heard over all lobes. Between attacks there were occasional wheezes with normal thoracic mobility and normal breath sounds. A roentgenogram of the chest and an electrocardiogram were both interpreted as being within normal limits.

CASE II. P. G. was a forty-one year old woman known to have had bronchial asthma for five years. Increased wheezing had occurred for one month which led to status asthmaticus that was unrelieved by the administration of sedatives, aminophyllin, prednisone, chlorpromazine and epinephrine. The patient had a history of hypersensitivity to iodides. Examination revealed an obese woman with a blood pressure of 140/90 mm. Hg. Her chest was filled with inspiratory and expiratory wheezes throughout. A roentgenogram of the chest showed accentuated bronchovesicular markings, the lung fields were otherwise clear and the heart was normal in size. An electrocardiogram taken during an attack revealed occasional premature beats, but the tracing was otherwise normal.

CASE III. K. Y. was a fifty-one year old woman who had had attacks of bronchial asthma for the last twenty-one years which were noted to be worse in early spring, late summer and preceding her menses. Prior therapy had consisted of the administration of potassium iodide, aminophyllin, ephedrine and phenobarbital. Examination revealed a moderately obese woman with a supple chest. Inspiratory and expiratory wheezes and rhonchi were heard all over the lung areas. A chest roentgenogram was interpreted as showing increased bronchovascular markings without evidence of infiltration; the heart was normal in size.

CASE IV. M. G. was a fifty-three year old woman who had had bronchial asthma for twenty-five years. For ten months prior to study asthma had been especially severe and had not responded to therapy which had included the administration of prednisone, phenobarbital, ephedrine, aminophyllin, isoproterenol and epinephrine. Examination of chest revealed diminished breath sounds with inspiratory and expiratory wheezes in all areas. A roentgenogram of the chest was interpreted as showing increased density of vascular markings and clear lungs. The heart was normal in size.

CASE V. M. C. was a forty year old woman who was known to have had bronchial asthma for twenty-two years. Asthmatic attacks had usually followed upper respiratory infections. The attack prior to study had not responded to vigorous therapy that had included the administration of prednisone, sedatives,

potassium iodide and isoproterenol. On physical examination the chest was supple with persistent inspiratory and expiratory wheezes heard throughout the chest. A roentgenogram of the chest was interpreted as hyperinflation with slightly flattened diaphragms and clear lungs. The heart was normal in size. An electrocardiogram was interpreted as being within normal limits.

CASE VI. J. T. was a thirty-seven year old man who had had bronchial asthma since the age of nine. There had been numerous hospital admissions in which the most effective therapy had been found to be vigorous sedation. The last attack had been refractory to therapy that had included the administration of steroids, isoproterenol and aminophyllin. The patient arrived in the emergency ward during the last attack in status asthmaticus. He was found to be cyanotic with a blood pressure of 110/90 mm. Hg. Chest was held in inspiratory position. Breath sounds were markedly diminished, only occasional wheezes were heard. An electrocardiogram revealed sinus tachycardia and low voltage. An x-ray film of the chest was reported as showing clear lungs with blunting of the left costophrenic angle. The heart was normal in size. Following therapy with oxygen and isoproterenol by intermittent positive pressure apparatus, breath sounds were normal and well heard, and the chest was supple.

CASE VII. C. C. was a sixty-five year old woman who had had attacks of asthma over the course of fifty-three years. Attacks were usually precipitated by respiratory infections or emotional trauma. She was admitted to the emergency ward in status asthmaticus. Her blood pressure was 100/80 mm. Hg. Her chest was virtually immobile and groaning inspiratory and expiratory wheezes were heard. A chest roentgenogram revealed old apical tuberculosis with fibrosis at the superior apical segment on the right. The lungs were otherwise clear and the heart was normal in size.

CASE VIII. R. L. was a fifty-one year old woman who had had asthma since the age of nineteen with increasing severity over the course of the last five years. Numerous medications including the administration of steroids had been decreasingly effective. Examination revealed normal vital signs. On auscultation inspiratory and expiratory wheezes with coarse rhonchi were heard over the entire surface of the chest. A roentgenogram of the chest revealed left apical fibrosis, low diaphragms, a heart normal in size, and no evidence of infiltration. An electrocardiogram revealed sinus tachycardia with left bundle branch block.

CASE IX. R. K. was a sixty-three year old man who had had asthma for twenty years. He had smoked two packs of cigarettes a day for the last fifty years. His latest attack of asthma was precipitated by an upper respiratory infection. Right-sided heart failure had been present for nine months which was well compensated by the administration of digitalis and mercurial diuretics. Examination revealed no clubbing or cyanosis; the chest was filled with persistent wheezes and rhonchi in all areas. Electrocardiogram revealed low voltage, normal sinus rhythm, and a strain pattern of the right side of the heart. A roentgenogram of the chest revealed the heart to be normal in size; the lungs were considered to be hyperinflated and the diaphragms were flattened. The hematocrit was 43.

CASE X. E. L. was a fifty-two year old man who had had recurrent attacks of bronchitis and wheezing for thirty years which was relieved most often by the administration of aminophyllin. He had smoked two packs of cigarettes a day for thirty-five years. On examination a dusky red color was noted over the face and neck with cyanosis of the nail beds. The chest was hyperinflated and fixed with low diaphragms. On auscultation inspiratory and expiratory wheezes were heard in all lung areas. Breath sounds were generally diminished. A roentgenogram of the chest was interpreted as showing a normal heart and lungs. An electrocardiogram revealed changes consistent with old posterior and anterior myocardial infarctions. The hematocrit was 58; arterial oxyhemoglobin saturation, 80 per cent; pCO_2, 46 mm. Hg; and pH, 7.40.

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Search for a Neuromuscular Blocking Agent in the Blood of Patients with Myasthenia Gravis*

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SEVERAL hypotheses have been proposed to explain the precarious status of neuromuscular transmission in the patient with myasthenia gravis. In one of these hypotheses transmission is considered to be inhibited by the action of a curariform agent which is present both at the neuromuscular junction and in the general circulation.

Several attempts have been made to demonstrate the existence of a circulating inhibitor of neuromuscular transmission in the blood of patients with myasthenia gravis, and both positive and negative results have been reported (see summary in [*1*]). With respect to these findings, the work of Bergh [*1*] indicates that the experimental conditions chosen by some investigators are such as to favor negative results. On the other hand, the positive results described in an early paper of Wilson and Stoner [*2*] and more recently those obtained by Struppler [*3*] are not entirely convincing for reasons which will be discussed later.

At this time it appears difficult to reach any definite conclusions as to the validity of the circulating inhibitor hypothesis. With the idea of providing additional evidence bearing on this point, we have assayed blood samples from myasthenic patients for the possible presence of an agent which inhibits neuromuscular transmission. In discussing the results obtained we include a consideration of factors which to us appear to be important in devising experimental tests for the detection of an unknown neuromuscular blocking agent.

METHODS

The twenty-two patients with myasthenia gravis who cooperated in this study showed therapeutic benefit from anticholinesterase therapy, and exhibited clinical signs characteristic of the disease. No attempt was made to select special cases; these patients showed a wide range in the severity of symptoms, and in the number and distribution of the muscles affected.

In the following tables and text we have used a code to designate: the subjects participating in this study, the number of the sample obtained from a particular subject, and the condition under which the sample was drawn. The abbreviations are:

C1 = normal control No. 1, etc.
MG1 = myasthenic patient No. 1, etc.
S1 = sample No. 1, etc.
AE = after exercise
BE = before exercise
NE = no exercise

In Table I we have listed information describing the myasthenic patients and the conditions under which blood samples were taken. Only one of these patients MG4, was known to have a thymoma. MG16 was shown postmortem to have an enlarged non-malignant thymus weighing 40 gm. Two patients with hyperthyroidism were under treatment with antithyroid drugs at the time blood samples were taken. MG3 was receiving propylthiouracil, MG5 was receiving methimazole. Trend in the severity of the disease when the sample was taken is based upon a study of the patient's condition during the three months prior to and the three months following the sampling.

From two of the normal control subjects, C2 and C4, two blood samples were drawn. C2-S2 was obtained 148 days after C2-S1, C4-S2 came sixty days after C4-S1.

Blood Sampling. From the antecubital vein 10 to 20 ml. of blood was drawn into a heparinized syringe. A cuff was then placed on the upper part of the arm, inflated to 200 mm. Hg and the patient or normal control subject was asked to pronate and supinate his

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TABLE I

PATIENTS WITH MYASTHENIA GRAVIS—CLINICAL AND BLOOD SAMPLING DATA

Patient, Sample, Code	Sex	Duration of Disease	Trend of Disease Severity at Sample Date	Distribution of Disease at Sample Date	Medication at Sample Date (mg. Mestinon®/ 24 hr.*)	Hrs. Post Medication at Sampling Time	Days Since Sample 1 (S1) Was Drawn
MG1-S1-AE. . . .	M	9 mo.	No change	Localized	300–375	13	. . .
MG1-S2-AE. . . .			No change	Localized	300–375	5	105
MG2-S1-AE. . . .	F	5 yr.	No change	Localized	450	10	. . .
MG2-S2-AE. . . .			Slight increase	Localized	750–900	*	98
MG3-S1-AE. . . .	M	3 mo.	Increasing	Generalized	840	3	. . .
MG3-S2-AE. . . .			Decreasing	Generalized	735	3	70
MG4-S1-AE. . . .	M	10 mo.	No change	Generalized	840	6	. . .
MG5-S1-AE. . . .	M	14 mo.	No change	Localized	0	. .	. . .
MG6-S1-AE. . . .	F	19 yr.	No change	Generalized	300	†	. . .
MG7-S1-AE. . . .	F	1 mo.	Decreasing	Generalized	945	12	. . .
MG8-S1-AE. . . .	M	3 yr.	Slight increase	Generalized	1800	12	. . .
MG8-S2-AE. . . .			Slight increase	Generalized	1800	†	3
MG9-S1-AE. . . .	M	12 yr.	No change	Localized	360	†	. . .
MG10-S1-AE. . .	M	9 yr.	No change	Generalized	1260–1470	11	. . .
MG11-S1-AE. . .	M	1 yr.	Decreasing	Localized	180	16	. . .
MG12-S1-AE. . .	M	1 mo.	No change	Localized	600	12	. . .
MG13-S1-AE. . .	F	1½ yr.	Decreasing	Generalized	270	12	. . .
MG14-S1-AE. . .	F	6 yr.	Increasing	Generalized	1260	17	. . .
MG14-S2-NE. . .			Increasing	Generalized	840	†	137
MG15-S1-AE. . .	M	1½ yr.	Decreasing	Generalized	210	3	. . .
MG16-S1-AE. . .	F	5 mo.	Increasing	Generalized	1200	12	. . .
MG16-S2-BE . . .			Increasing	Generalized	1300	†	16
MG16-S3-AE. . .			Increasing	Generalized	1300	†	16
MG17-S1-BE . . .	F	17 yr.	Slight decrease	Generalized	700	11	. . .
MG17-S2-AE. . .			Slight decrease	Generalized	700	11	0
MG18-S1-AE. . .	F	4 yr.	Decreasing	Generalized	225	24	. . .
MG19-S1-AE. . .	F	7 mo.	Increasing	Generalized	1680	6	. . .
MG19-S2-NE. . .			Decreasing	Generalized	1680	6	42
MG20-S1-NE. . .	F	20 yr.	No change	Generalized	840	8	. . .
MG21-S1-NE. . .	M	3 yr.	Decreasing	Generalized	450	12	. . .
MG22-S1-NE. . .	F	15 yr.	Decreasing	Generalized	300	12	. . .

* Medication for most patients was pyridostigmine (Mestinon) alone. MG6, MG11 and MG20 were receiving ambenonium (Mytelase). MG16 at the S2 sample date was receiving pyridostigmine plus ambenonium. MG13 was receiving pyridostigmine plus neostigmine. For these cases the total drug intake per twenty-four hours is recalculated as pyridostigmine, by use of the following equivalents: 60 mg. pyridostigmine = 15 mg. neostigmine = 7.5 mg. ambenonium.

† Datum not recorded in clinical records. Period of medication withdrawal estimated at ten to sixteen hours.

arm for four minutes. At the end of this time 10 to 20 ml. of blood was withdrawn, as before, from the now exercised arm. In most cases, in order to obtain a full sample, it was necessary to reduce the cuff pressure to 50 mm. Hg. The simplifying modifications introduced in later experiments were omission of the heparin (Tables III, IV) and of exercise. (Table IV.)

Within one hour after drawing the blood, the sample was centrifuged and plasma or serum was drawn off. From this point, until the bioassay was performed, the sample was kept at 4°C. or below. Control blood samples were obtained in a similar way from normal healthy male laboratory personnel (eight subjects) whose ages ranged from twenty-two to forty-nine years, and also from the normal female cousin (C1) of one of the myasthenic patients (MG2).

Tests for neuromuscular block were performed using an excised frog (Rana pipiens) sartorius muscle with its attached motor nerve. In performing the dissection, the distal tendon was tied with a short loop of silk thread. The proximal attachment of the muscle to the pubis was left intact. Each femur was dissected free of its attachment to the pelvic girdle and the ilia were cut close to the acetabulum. A fresh preparation was used for each test of plasma or serum.

The muscle was mounted as shown in Figure 1 for isometric recording of twitch and tetanus tension. A stainless steel pin driven through the acetabulum

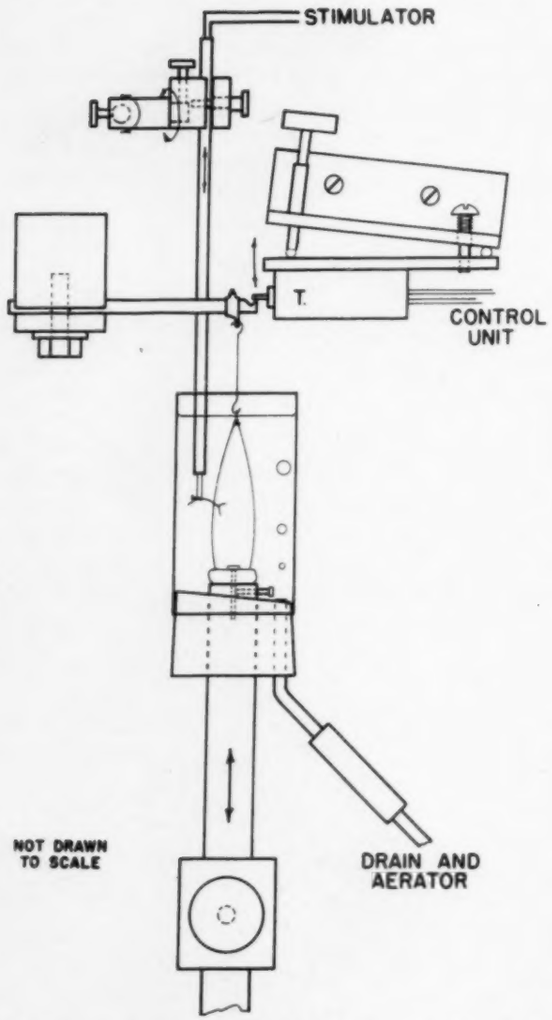


FIG. 1. Diagram of apparatus showing muscle chamber, stimulating electrodes, isometric myograph, transducer (T) and transducer manipulator.

was held firmly in a rigid vertical stainless steel rod. The loop of silk thread tied to the distal tendon was coupled, by means of a stainless steel wire, 0.5 mm. in diameter, with hooked ends, to a clamped steel drill rod which served as an isometric lever (natural period 900 c.p.s.). Contractions of the muscle produced small movements of this rod and these displacements were converted into proportional electrical signals by means of an RCA 5734 mechanoelectronic transducer. (Fig. 1.) The signals at the output of the transducer were displayed using the D.C. channel of a Du Mont 304 H oscillograph. In some experiments muscle tension was determined by visual observation of the oscillogram, in other experiments a photographic recording was employed.

The stainless steel pedestal on which the acetabulum was mounted was lowered so that the muscle was stretched to approximately 110 per cent of its normal resting length in the body. A parallel pair of Ag.AgCl electrodes, insulated except for their hook shaped ends, were positioned 2 to 3 mm. from the muscle close to the point of emergence of the motor nerve. The nerve was gently wrapped two or three times around the electrodes, and its adhesive qualities sufficed to keep it in this position. The nerve was stimulated electrically with square wave pulses 0.1 millisecond in duration and two and a half times the intensity required to produce a maximal twitch. Single stimuli and trains of stimuli were used as specified under "Results." Control experiments ruled out the possibility of direct stimulation of adjacent muscle fibers.

At this stage, the solution chamber (capacity 30 ml.) was raised into position and filled with Ringer solution, pH 7.4, having the following composition:

Na^+	116.55 mM./L.
K^+	2.5 mM./L.
Ca^{++}	1.8 mM./L.
Cl^-	117.1 mM./L.
$H_2PO_4^-$	0.45 mM./L.
$HPO_4^=$	2.55 mM./L.
glucose	5.56 mM./L.

Air was bubbled through the bath via a small inlet in the rubber stopper forming its base. The bath temperature, governed by the prevailing ambient temperature, ranged from 21 to 28°C., but in individual experiments the maximum temperature variation was 2°C.

By means of a split beam micromanipulator (Fig. 1) the transducer was lowered until its driving pin contacted the knife edge of the isometric lever. The transducer was then lowered further so that its driving pin would remain in contact with the knife edge throughout all displacements of the lever produced by contraction of the muscle.

During the control period, which was usually about one hour in duration, the muscle was stimulated according to a specified schedule, e.g., 50 stimuli/second for 0.28 seconds, repeated at ten minute intervals. Once set, the stimulation procedure was unchanged for the remainder of the experiment. In general, at the start of equilibration, the muscle tension diminished with each successive stimulation, but finally a steady value was reached. Control experiments indicate that when finally achieved, the steady state tension was maintained within ± 4 per cent for six hours, the maximum rate of change never exceeding 4 per cent of the steady state value/hour. During this equilibration period the Ringer solution was changed at twenty minute intervals.

When there was reasonable assurance that the muscle had reached a steady state, the bath was drained and filled with 20 to 25 ml. of a mixture of Ringer solution plus plasma or serum in stated proportions. Air was again bubbled through this solution and stimuli were applied to the nerve according to the

schedule set during the control period. The test period varied from twenty to 231 minutes during which time the bathing solution was not changed. At the end of this period the muscle chamber was drained, flushed three times, and finally filled with Ringer solution which was changed at twenty minute intervals. The contractile responses were usually followed until a steady state was reached once again.

For experiments, the results of which are given in Table IV, a different technic was used in order to make possible the simultaneous recording of a muscle twitch and also the resting and action potentials of single muscle fibers by means of an intracellular electrode. In this case, the muscle was stretched in the horizontal plane, in a Petri dish containing appropriate solutions. The pin, driven through the acetabulum as previously described, was gripped in a horizontally adjustable stainless steel rod. The distal tendon was coupled to an isometric myograph and recorder basically like that described earlier. In this case however, a duraluminum yoke was used to transmit the force of the twitches over the rim of the Petri dish to the myograph drill rod. The recording from single muscle fibers was carried out as described in another paper [*4*].

In this final series of experiments the shallow muscle bath was aerated by means of a fine stream of air bubbles. Since no mixing was employed, the method was not very effective, but diffusion of air into the shallow bath provided additional oxygenation. Also, in these experiments only single twitches were elicited, thus keeping the oxygen requirement of the muscle low.

In certain cases repeat assays were carried out on an individual sample, which meant successive exposures of that particular sample to fresh nerve-muscle preparations, in addition to aging in storage. We did not, in other words, use separate aliquots of a particular sample for the repeat assays.

RESULTS

For the first series of experiments (Table IIA) plasma was collected from patients with myasthenia gravis and normal control subjects after exercise as described in the section on "Methods." The samples were diluted with Ringer solution so that the plasma concentration was 28 per cent. Additional experiments were conducted (Table IIB) using higher concentrations of plasma and serum obtained from other myasthenic patients. The samples in this series (Tables IIA and B) were tested within four hours after they were drawn, with one exception; MG1-S1-AE sample was one day old at the time of the test. All samples were held at 4°C. until transferred to the muscle chamber.

For the experiments of Table IIA and B, the muscle-nerve preparation was equilibrated in Ringer solution (changed every twenty minutes) during which time the nerve was stimulated at ten minute intervals as follows: a single stimulus was first applied and followed thirty seconds later by a repeated stimulus, frequency fifty/second, train duration 280 milliseconds. This stimulation procedure was maintained throughout the remainder of the experiment. The preliminary equilibration was considered to be complete when the maximum twitch and tetanus tensions remained reasonably constant for three or more successive ten minute intervals. The steady state tension served as a baseline control for the measurement of changes produced during the subsequent test and recovery periods. During the test period, the muscle-nerve was immersed in plasma-Ringer solution or serum-Ringer solution mixture (not changed) for forty to 231 minutes. Following the test period the bath was drained and the preparation was washed and allowed to recover in Ringer solution (changed every twenty minutes) for sixty minutes or longer.

The data representing fourteen determinations using 28 per cent plasma obtained from twelve patients with myasthenia gravis, and four determinations using 28 per cent plasma from normal control subjects, are summarized in Table IIA. Shown in Table IIB are results from three additional myasthenic patients. The latter data were obtained using higher concentrations of plasma or serum, as stated.

With respect to the maximum tetanus tension measured after forty minutes exposure to plasma-Ringer solution mixture, it can be seen that for nine of the twelve samples from myasthenic patients listed in Table IIA, the results are within the normal range. The plasma samples MG1-S1-AE, MG2-S1-AE and MG3-S1-AE caused a reduction in tetanus tension to a point below the control range. As regards the twitch tension, again compared at the end of forty minutes, none of the samples caused depression to a point well below the control range.

An unexpected augmentation of the single twitch was produced by several plasma samples, MG3-S2-AE (at 36 per cent), MG4-S1-AE, MG5-S1-AE, MG6-S1-AE, MG8-S2-AE, MG9-S1-AE and MG10-S1-AE. The latency of this effect averaged twenty-four minutes with a range of eight to forty-five minutes. For MG4-

TABLE IIA

EFFECT OF DILUTED PLASMA (28 PER CENT) FROM TWELVE PATIENTS WITH MYASTHENIA GRAVIS AND FOUR NORMAL CONTROL SUBJECTS ON TETANUS AND TWITCH TENSION OF INDIRECTLY STIMULATED FROG SARTORIUS MUSCLE

Patient, Sample, Code	Duration of Plasma-Ringer Solution Test (min.)	Maximum Tetanus Tension—% of Initial Control				Maximum Twitch Tension—% of Initial Control				Bath Temperature (°C.)
		After 10 Min. in Plasma-Ringer	After 40 Min. in Plasma-Ringer	At end of Plasma-Ringer Test	After 60 Min. Recovery in Ringer	After 10 Min. in Plasma-Ringer	After 40 Min. in Plasma-Ringer	At End of Plasma-Ringer Test	After 60 Min. Recovery in Ringer	
Patients with Myasthenia Gravis										
MG1-S1-AE....	40	94	80	80	99	93	80	80	83	27
MG2-S1-AE....	50	93	84	82	93	82	69	67	83	28
MG3-S1-AE....	160	80	66	37	58*	82	74	58	84*	27
MG3-S2-AE....	231	96	95	108†	106	94	94	122†	83	24
MG4-S1-AE....	164	95	92	72	69*	100	172	140	170*	29
MG5-S1-AE....	121	93	92	93	92	81	146	164	94	25
MG6-S1-AE....	150	94	94	92	90*	105	135	142	159*	27
MG7-S1-AE....	138	95	94	85	82	88	84	75	75	27
MG8-S1-AE....	141	94	93	89	89	91	85	77	85	27
MG8-S2-AE....	70	98	100	100	96	200	196	200	85	25
MG9-S1-AE....	142	95	95	96	100	95	115	140	92	23
MG10-S1-AE...	143	98	96	96	93	94	122	88	88	24
MG11-S1-AE...	130	94	94	91	....	86	73	76	‡	25
MG12-S1-AE...	139	93	92	86	86	85	74	64	74	25
Average.....	130	94	91	86	94	98	109	107	84	26
Normal Control Subjects										
C1-S1-AE.....	140	97	95	89	91	85	79	67	83	28
C2-S1-AE.....	150	95	94	83	77	90	78	71	80	26
C3-S1-AE.....	138	93	93	85	92	77	71	62	77	28
C4-S1-AE.....	139	96	97	94	98	88	87	85	95	25
Average.....	142	95	95	88	90	85	79	71	84	27

* Muscle placed in control plasma-Ringer solution, instead of Ringer solution, during this period. This datum not included in average.

† During the final eighty-eight minutes of the test period the plasma concentration was raised to 36 per cent.

‡ No recovery data obtained at sixty minutes.

TABLE IIB

EFFECT OF HIGHER CONCENTRATIONS OF PLASMA OR SERUM OBTAINED FROM THREE PATIENTS WITH MYASTHENIA GRAVIS ON TETANUS AND TWITCH TENSION OF INDIRECTLY STIMULATED FROG SARTORIUS MUSCLE

MG13-S1-AE...	134	93	93	93	95	82	81	71	89	24
MG14-S1-AE...	139	87	73	72	65	75	64	49	55	24
MG15-S1-AE...	69	94	95	96	97	85	80	78	79	24

Concentrations: MG13—42 per cent plasma, MG14—55 per cent serum, MG15—32 per cent serum.

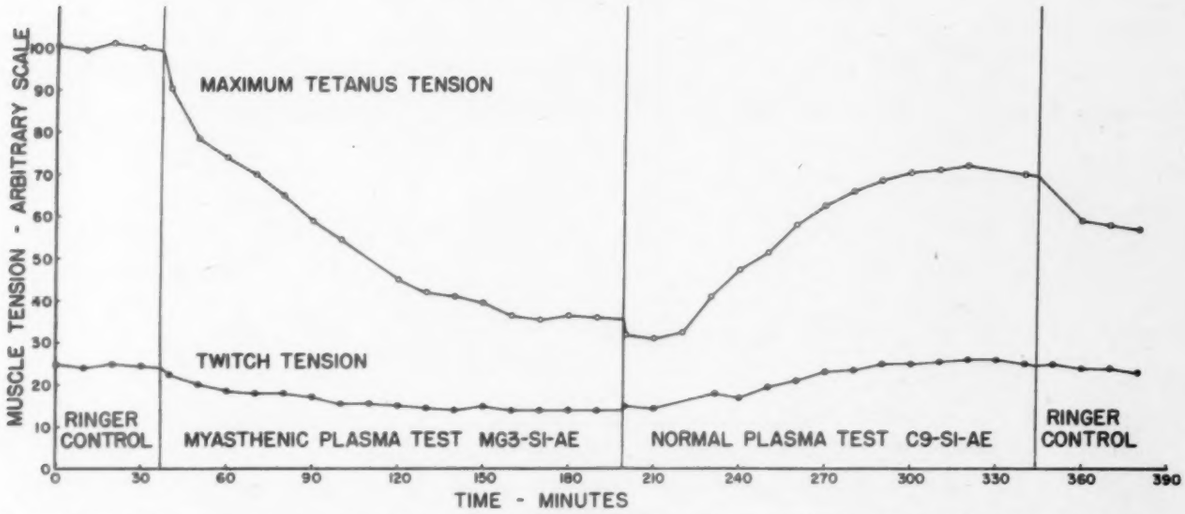


FIG. 2A. Plot of maximum tetanus tension and twitch tension of an indirectly stimulated sartorius muscle versus time during: (a) preliminary Ringer solution control period, (b) 160 minutes exposure to 28 per cent myasthenic patient's plasma (MG3-S1-AE)-Ringer solution, (c) 146 minutes exposure to 28 per cent normal control plasma (C9-S1-AE)-Ringer solution, (d) Ringer solution recovery period. Stimulation procedure: at each ten minute interval, single stimulus followed thirty seconds later by stimulus train 280 milliseconds in duration at frequency of 50/second. For further details see Tables I, IIA and the text.

S1-AE, MG5-S1-AE and MG8-S2-AE, the twitch augmentation, once it appeared, increased to the maximum within ten minutes and thereafter was steadily maintained. For MG3-S2-AE, MG6-S1-AE and MG9-S1-AE, twitch augmentation increased more slowly. For MG10-S1-AE the augmentation was small and variable. In all cases in which the nerve-muscle preparation was returned to Ringer solution twitch augmentation disappeared within ten minutes and the twitch tension remained steady thereafter.

In the two tests involving MG4-S1-AE and MG6-S1-AE, immediately after removal of the mixture composed of plasma from the particular myasthenic patient and Ringer solution, the nerve-muscle was placed in 28 per cent normal plasma-Ringer solution mixture. This change in bathing solution did not reduce the twitch augmentation which thereafter remained without decrement at or above the peak value achieved during the preceding test period. One of these experiments lasted sixty minutes, the other 108 minutes.

Results illustrating the general nature of the experiments of Table IIA are given in Figures 2A and B.

The results of three exploratory experiments presented in Table IIB show that only MG14-S1-AE (55 per cent serum) produces an appreciable depression of tetanus and twitch tensions. In the absence of control experiments carried out using 55 per cent normal serum-Ringer solution mixture, no final statement as to the significance of this result can be made.

Two additional facts which emerge from the results of this first series of experiments are: (1) the depression in tetanus tension produced by plasma from patients with myasthenia gravis has a relatively slow time course (Fig. 2A), (2) exposure of the nerve-muscle preparation either to plasma from patients with myasthenia gravis or to serum from normal subjects produces changes which are not completely reversible when the preparation is allowed to recover in Ringer solution. (Tables IIA and B.)

The results of the experiments just described led us to perform a second series of experiments in which the conditions were altered. The idea was to try to bring out more clearly any differences between the effects produced by serum from patients with myasthenia gravis and those produced by serum from control subjects. One modification was to increase the serum concentration to 50 per cent (with one minor exception as stated in Table III). The stimulation procedure was also changed, in order to set conditions under which neuromuscular transmission would become more precarious and

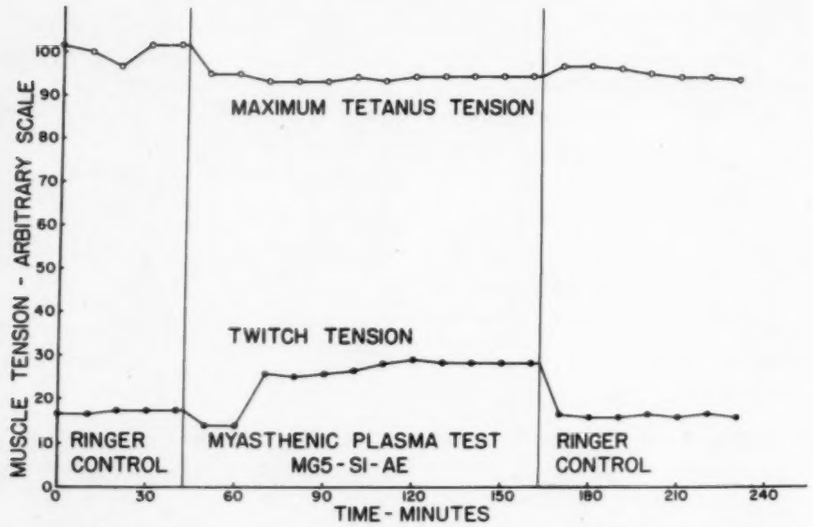


FIG. 2B. Plot of maximum tetanus tension and twitch tension of an indirectly stimulated sartorius muscle versus time during: (a) preliminary Ringer solution control period, (b) 121 minutes exposure to 28 per cent myasthenic patient's plasma (MG5-S1-AE)-Ringer solution, (c) Ringer solution recovery period. Stimulation procedure: at each ten minute interval, single stimulus followed thirty seconds later by stimulus train 280 milliseconds in duration at frequency of 50/second. For further details see Tables I, IIA and the text.

therefore more easily interrupted by a blocking agent which might be present in serum from myasthenic patients. We assumed that this technic would enable us to detect a blocking agent which might be present in a subcritical concentration, that is to say, a concentration insufficient to cause block at a neuromuscular junction at which a normal safety margin in transmission exists. In pursuit of improved experimental conditions we used as a guide the sensitivity of the neuromuscular preparation to transmission block by d-tubocurarine, and finally arrived at the following procedure. The motor nerve was stimulated at a frequency of 150/second for a one to three second period and this tetanus was repeated at five to fifteen minute intervals. In any individual experiment the duration of the tetanus was adjusted so that at its close the muscle tension had fallen to approximately 50 per cent of the peak value developed after the start of the stimulus train. The period between tetanic contractions was varied until successive stimulations gave essentially constant responses.

It was found that the tension measured at the end of the tetanus (roughly 50 per cent of the peak value) could be significantly depressed if d-tubocurarine, 0.1 mg./L., was added to the bath. This concentration of d-tubocurarine left the peak tetanus tension unaffected. Thus in regard to the detection of d-tubocurarine, our modified procedure gave a fivefold or greater increase in sensitivity compared with the technic used for experiments cited in Tables IIA and B.

The results obtained using serum from six patients with myasthenia gravis and one normal control subject are presented in Table III. A plot of one of these experiments (MG19-S1-AE) is shown in Figure 3. Several muscle tetanus records obtained during this experiment are shown in Figure 4. In Table III the peak tetanus tension shown for the control period was measured at a time when the nerve muscle had reached a steady state. The value obtained was set at 100 units on an arbitrary scale. All subsequent measurements of peak tetanus tension were referred to this scale. The end tetanus tension is expressed as percent of the corresponding peak tetanus tension.

A significant depression of peak tetanus tension was produced by only two serum samples both of which were obtained from a single myasthenic patient, MG19. Another feature of the serum obtained from MG19 is that it had an irreversible effect on the nerve-muscle preparation. The basis for this statement is the fact that after return of the preparation to Ringer solution the peak tetanus tension showed no sign of rising, but instead fell slightly to a lower value, finally reaching a plateau at which it remained thereafter.

TABLE III

EFFECT OF SERUM FROM 6 PATIENTS WITH MYASTHENIA GRAVIS AND 1 NORMAL CONTROL SUBJECT ON TETANUS TENSION PRODUCED DURING BRIEF HIGH FREQUENCY INDIRECT STIMULATION OF FROG SARTORIUS MUSCLE

Patient, Sample, Code	Age of Sample (days)	Muscle in Serum Ringer (min.)	Stimulation Parameters			Muscle Tension*					
						Control Period (Ringer)		End of Test Period (Serum-Ringer)		After 40 min. Recovery (Ringer)	
			Frequency (stim./sec.)	Train Duration (sec.)	Interval between Tetanic Contractions (min.)	Peak Tetanus	End Tetanus as % of Peak Tetanus	Peak Tetanus	End Tetanus as % of Peak Tetanus	Peak Tetanus	End Tetanus as % of Peak Tetanus
Patients with Myasthenia Gravis											
MG1-S2-AE†	0	34	200	1.0	5	100	32	98	53	95‡	21‡
MG1-S2-AE† (repeat)	1	20	300	5.0	5	100	18	109	20	85	13
MG2-S2-AE	12	22	150	1.5	10	100	64	98	83	103	62
MG16-S1-AE	0	34	150	3.0	12	100	41	86	61	90	32
MG16-S1-AE (repeat)	1	58	150	1.5	15	100	56	100	79	104	66
MG16-S2-BE	1	29	150	1.25	15	100	69	96	79	96	68
MG16-S3-AE	4	29	150	2.0	10	100	67	100	79	102	68
MG17-S1-BE	0	28	150	1.5	10	100	79	97	84	98	73
MG17-S2-AE	1	28	150	1.5	10	100	74	96	84	100	79
MG18-S1-AE	0	55	150	1.5	15	100	66	100	79	104	62
MG19-S1-AE	0	37	150	2.0	8	100	54	70	70	60	42
MG19-S1-AE (1st repeat)	1	22	150	1.5	10	100	65	68	69	61	57
MG19-S1-AE (2nd repeat)	3	22	150	1.5	10	100	58	73	74	68	65
MG19-S1-AE (3rd repeat)	17	40	150	1.5	10	100	63	81	83	79	76
MG19-S2-NE	1	29	150	1.5	10	100	66	66	82	63	68
Normal Control Subjects											
C4-S2-NE	0	37	150	2.0	10	100	69	83	76	83	76
C4-S2-NE (repeat)	1	38	150	1.5	10	100	72	91	81	95	66

* During the control period, when the nerve-muscle had reached a steady state, the measured value of peak tetanus tension was set at 100 units on an arbitrary scale. All subsequent peak tetanus tension measurements were referred to this scale. Each value of end tetanus tension is expressed as a per cent of the peak tetanus tension measured at the same moment.

† 45 per cent serum.

‡ After twenty-four minutes in Ringer solution.

This depressant action of the MG19-S1 serum sample was not diminished by three days' storage at 4°C. which was interrupted by use in two additional assays (first and second repeat). However, after a total of seventeen days' storage this sample appeared to have lost some activity, as shown by the results of the third repeat assay. The MG19-S2-NE sample is considered to be about as active as MG19-S1-AE.

As mentioned earlier, the end tetanus tension was depressed by low concentrations of d-tubocurarine which left the peak tetanus tension unchanged. We speculated that similar results might be obtained if the serum from myasthenic subjects contained a low concentration of neuromuscular blocking agent. It was therefore somewhat surprising to find that all serum samples from myasthenic patients and the control caused an *increase* in end tetanus tension. The magnitude of the effect varied with different samples (Table III, compare column 8 with column 10). In three experiments in which early measurements were made, the latency for this augmentation must have been less than two minutes. The maximum augmentation is reached in approximately ten minutes, and once reached this level is well maintained. It is interesting to note that in the tests in which MG19 serum samples were used, facilitation of end tetanus tension occurred as usual, and the extent of the facilitation was not altered by the appreciable reduction in peak tetanus tension, which developed more slowly.

For the final series of experiments we decided to investigate, simultaneously, the variation of twitch tension and the membrane potentials

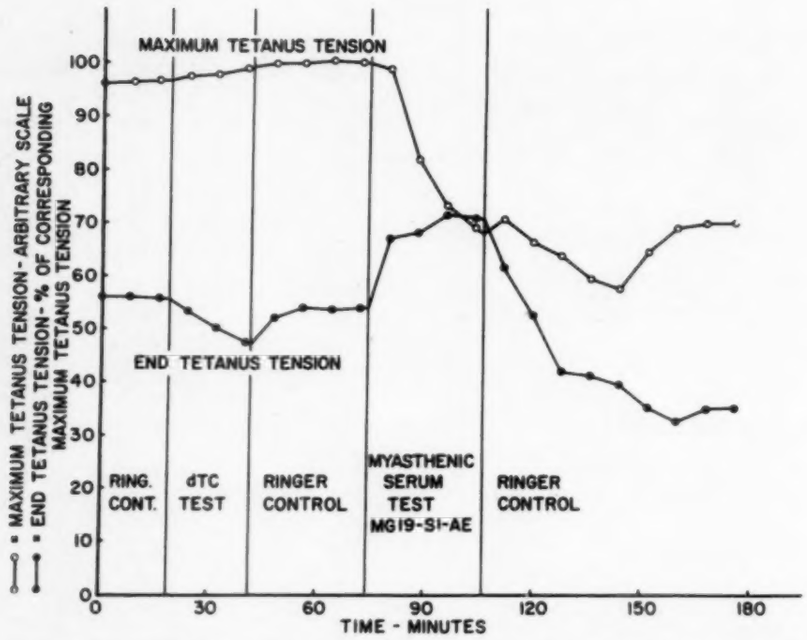


FIG. 3. Plot of maximum tetanus tension and end tetanus tension of an indirectly stimulated sartorius muscle versus time during: (a) preliminary Ringer solution control period, (b) application of Ringer solution containing d-tubocurarine 0.1 mg./L., (c) second Ringer solution control period, (d) thirty-seven minutes exposure to 50 per cent myasthenic patient's serum (MG-19-S1-AE)-Ringer solution, (e) Ringer solution recovery period. Stimulation procedure: at eight minute intervals, stimulus train two seconds in duration at frequency of 150/second. During the second Ringer solution control period, at a time when the tension readings were stabilized, the measured value of peak tetanus tension was set at 100 units on an arbitrary scale as shown. All preceding and succeeding peak tetanus tension measurements were referred to this scale. Each value of end tetanus tension is expressed as per cent of the peak tetanus tension measured at the corresponding moment. For further details see Figure 4, Tables I, III and the text.

of single muscle fibers of the sartorius muscle when the nerve-muscle preparation was exposed to 50 per cent serum-Ringer solution mixtures. In these tests the muscle was placed in the horizontal position in a shallow pool of solution (see "Methods"), and single stimuli were delivered to the motor nerve at ten second intervals throughout the entire course of each experiment. An exception to this procedure was an experiment conducted with MG19-S2-NE in which the stimulus frequency was 1 per minute. All serum samples except MG19-S2-NE were tested two to four hours after withdrawal. MG19-S2-NE was tested three days after withdrawal and this sample had already been used once in an earlier assay. (Table III.) The temperature of the bath ranged from 22 to 25°C., averaging 23°C.

Table IV shows that the averages of the data obtained with serum from myasthenic patients do not differ greatly from those obtained with serum from control subjects. Several samples caused a twitch augmentation with a latency of one to two minutes. The peak in twitch augmentation was reached in three to ten minutes and once reached was steadily maintained for the duration of the serum-Ringer solution test period. This augmentation effect was considerable with MG20-S1-NE, MG22-S1-NE, C2-S2-NE and C5-S1-NE. It was small with MG21-S1-NE and C6-S1-NE.

Two of the samples from control subjects, C6-S1-NE and C7-S1-NE, caused a reduction in twitch tension which was fully established after ten minutes, the time at which the first reading was taken. Thereafter the twitch tension remained depressed at a constant level. On return to Ringer solution, in both of these experiments the tension rose appreciably during the first minute and finally it stabilized at 86 to 88 per cent of the control value.

The results obtained with serum samples from two myasthenic patients, MG19-S2-NE and MG14-S2-NE, differ from all other experiments. MG19-S2-NE was tested on three occasions over a five day period, but only the results of the first experiment are included in Table IV. This sample caused a prompt (latency

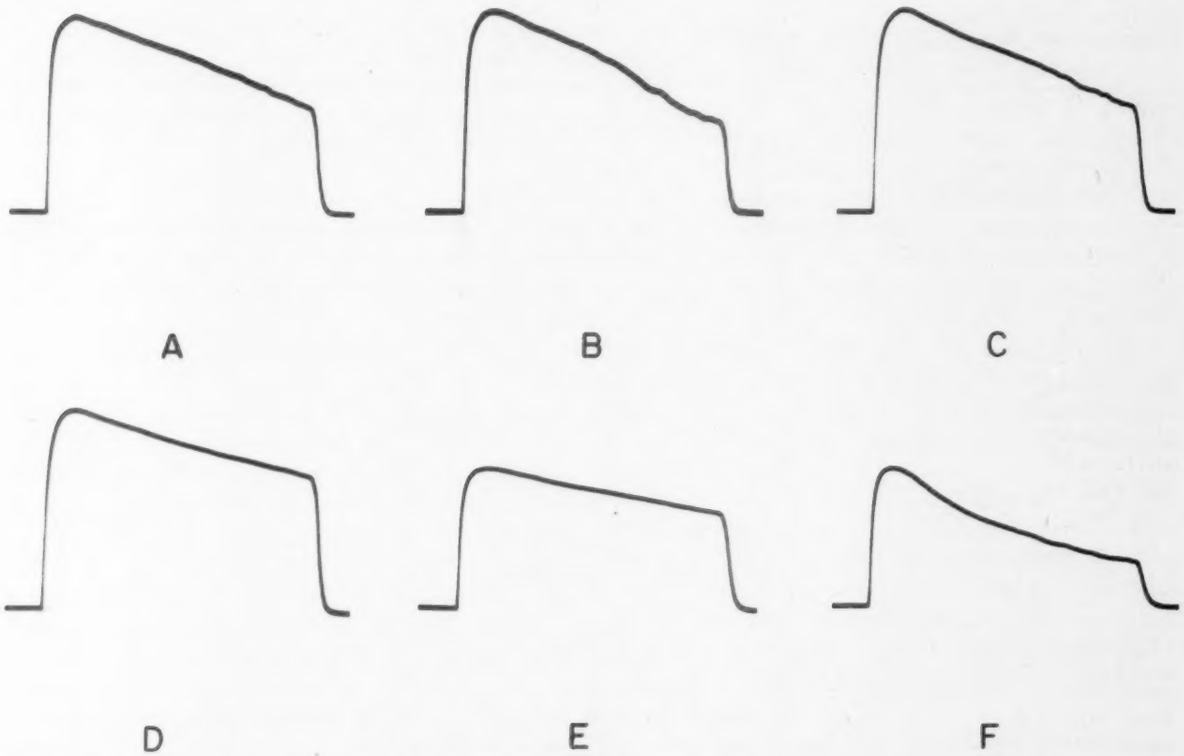


FIG. 4. Six myograms recorded during the experiment shown in Figure 3. A, during first Ringer solution control (elapsed time sixteen minutes). B, during application of Ringer solution containing d-tubocurarine 0.1 mg./L. Fall in end tetanus tension, no change in peak tetanus tension (elapsed time forty minutes). C, during second Ringer solution control period (elapsed time seventy-two minutes). D, after six minutes exposure to 50 per cent myasthenic patient's serum (MG19-S1-AE)-Ringer solution (elapsed time eighty minutes). E, same as D but after total of thirty minutes exposure to 50% myasthenic patient's serum-Ringer solution (elapsed time 104 minutes). F, after sixty-two minutes recovery in Ringer solution (elapsed time 168 minutes).

two minutes) reduction in twitch tension and thereafter the tension continued to fall at a rapid rate. The MG14-S2-NE sample also produced a fairly rapid progressive fall in twitch tension but in this case the latency was about fifteen minutes.

In these experiments (Table IV), at a time when the twitch tension was declining rapidly, transmembrane potential measurements were made from surface fibers of the muscle. Resting potentials were low, reaching 15 to 20 mv. for many cells and, as might be expected, no action potentials were recorded in these cells following nerve stimulation. For MG14-S2, at the time of initiation of the rapid decline of the twitch tension, transmembrane potentials were recorded at six endplates. Resting potentials were normal or moderately depressed, and endplate potentials produced by a single nerve volley showed an abnormally low rate of rise but their amplitude was still sufficient to cause initiation of propagated action potentials. The action potentials thus recorded were usually subnormal in amplitude.

At the time when low resting potentials were recorded many surface muscle fibers became cloudy, started to lose their normal appearance, and finally began to disintegrate at various loci bearing no discernible relation to the neuromuscular junctions. At this stage, on driving the tip of the microelectrode two to three cells deeper into the interior of the muscle, fibers were impaled whose resting potentials were in the normal range. These interior cells showed conducted action potentials following stimulation of the motor nerve.

To us the preceding facts indicated that a cytolytic agent of poor penetrating power was present in serums MG14-S2 and MG19-S2. No serum from control subjects produced such changes during the serum assay period. However, a "delayed" cytolysis was produced in the

TABLE IV

EFFECT OF SERUM FROM FIVE PATIENTS WITH MYASTHENIA GRAVIS AND FIVE NORMAL CONTROL SUBJECTS ON TWITCH TENSION OF INDIRECTLY STIMULATED FROG SARTORIUS MUSCLE

Patient, Sample, Code	Duration of Serum-Ringer Solution Test (min.)	Maximum Tension of Single Twitch % of Initial Control Period Tension			
		After 10 Min. in Serum-Ringer	After 40 Min. in Serum-Ringer	After 10 Min. in Ringer	After 40 Min. in Ringer
Patients with Myasthenia Gravis					
MG20-S1-NE	47	127	119	117	88
MG21-S1-NE	52	104	99	106	85
MG22-S1-NE	45	142	138	130	89
MG19-S2-NE*	40	84	64	69	66
MG14-S2-NE	50	102	86	84	66
Average	47	112	101	101	79
Normal Control Subjects					
C5-S1-NE	44	112	110	115	89
C6-S1-NE	44	106	100	118	92
C2-S2-NE	48	139	130	†	†
C7-S1-NE	46	80	77	91	86
C8-S1-NE	43	87	83	102	88
Average	45	105	100	106	89

* Repeat determination, sample used in prior test, see Table III.
† Lost because of apparatus failure.

muscle which had been exposed to one of the control samples, C7-S1-NE. The effect appeared after this muscle had recovered in Ringer solution for forty-three minutes, at which time a few partially disintegrated surface fibers were observed. At the end of sixty-eight minutes recovery in Ringer solution, 16 per cent of the surface fibers had partially disintegrated. No other serum from control subjects in this series produced "delayed" cytolysis.

COMMENT

Before turning specifically to the discussion of the results obtained in our study, we wish to comment briefly on certain points which we believe bear upon a search for a neuromuscular blocking agent in the blood of patients with myasthenia gravis.

Conditions Under Which Blood Sample is Drawn, and Treatment of Sample Up to Time it is Used in Any Assay. The results of Mary Walker's [5] oft quoted experiments indicate that a neuromuscular blocking agent is discharged into the blood trapped within an exercised occluded ischemic limb of the patient with myasthenia gravis. The tissue hypoxia produced in these experiments might (1) favor production of a blocking agent, (2) favor activation of a blocking agent already present in inactive form, or (3) cause release of a blocking agent ordinarily bound to tissue. In any case, one must ask whether or not these results are peculiar to the person with myasthenia gravis.

Muscles exercised under hypoxic conditions release many substances, and it is conceivable that some of these might be mild inhibitors of neuromuscular transmission. The experiments of Schmidt and Chase [6], although not as perfectly controlled as one would wish, support this view. In the normal person the neuromuscular transmission process has a large safety margin, and hence it is not likely to show complete block when mild inhibitors are present. However, in the myasthenic patient neuromuscular transmission has little or no safety margin, and being therefore precarious it could be easily interrupted by weak inhibitors of the type indicated. In short, until this line of rea-

soning can be ruled out, the results of Walker's experiments need not be considered as having fundamental significance with respect to the etiology of myasthenia gravis. It is worth noting that this is essentially the position taken by Walker in response to a question dealing with this matter [*5*].

Wilson and Stoner [*2*] emphasized the importance of exercise in increasing the muscle tension depressing power of serum samples, stating that "In the group before exercise the depression of muscle contraction was never greater than 25 per cent." Wilson [*7*] informed us that several methods of exercise were used: "In some, the blood was collected before and after exercise of the arm with an occlusion cuff. Other patients were put on a static bicycle and after 10 or 15 minutes continuous exercise, blood was taken from an arm vein." Unfortunately we cannot determine from Wilson and Stoner's data whether one or the other of their exercise methods is more effective, and this is a point of some consequence when Struppler's work is considered [*3*].

In a more recent paper Struppler [*3*] places great emphasis on exercise under ischemic conditions as being an important factor in increasing the concentration of a humoral neuromuscular blocking agent in myasthenia gravis. His evidence is in part based on determinations of the fall in the amplitude of neurally initiated compound muscle action potentials in the patient. He states in this connection that with venous occlusion alone, the fall in action potential amplitude is much less frequently found, and compared with complete ischemia, is much smaller in extent, but he gives no numerical comparison.

Struppler presents experiments which to him argue against the possibility that the products of anaerobic muscular activity are in any way responsible for inhibition of neuromuscular transmission. In their presently described form, we cannot accept these experiments as conclusive. His statements indicate to us that the amount of d-tubocurarine which was administered to the three normal subjects did not place their neuromuscular transmission in a precarious state, i.e., having a reduced safety margin comparable with that found in patients with myasthenia gravis. Hence his action potential measurements are not likely to reveal the presence of a subliminal neuromuscular blocking effect produced possibly by anaerobic metabolic end products. Nonetheless, the general conception of these curare experiments is critical, and a more complete exploration along such lines is very much needed.

Extending the argument further, Struppler stated that with healthy subjects serum obtained from the ischemic arm (no exercise is stated to have been performed), when used in his animal experiments, never caused a fall in muscle action potential (dog gastrocnemius muscle *in vivo*), or loss of tension output (mouse phrenic nerve-diaphragm *in vitro*). For these experiments, and others, Struppler presents typical or maximal results. Presentation of the data in tabular form would have been more helpful in permitting us and others to reach his conclusions independently.

Our own data give no supporting evidence that for myasthenic patients, exercise under ischemia increases the neuromuscular blocking action of plasma obtained from the involved arm. However, we do not by any means regard our limited experiments as really critical on this point, and we believe that the entire matter is still unsettled.

After blood samples have been drawn from a myasthenic patient there is always a possibility that the active agent supposed to be present might undergo inactivation. In our experiments we stored all samples at 4°C. until used and in many cases we tested them with only a few hours delay. Our only line of evidence indicating that this is a safe procedure is the following: If we assume that the depression of muscle tension produced by certain blood samples (e.g., MG19-S1, Table III) indicates the presence of an active agent, then one must conclude that this agent was preserved in our hands because it survived three twenty-two to forty minute exposures to frog muscle at 23°C. and more than three days' storage at 4°C.

Test Preparation Used in Serum or Plasma Assay, and Experimental Conditions Under which Assay is Performed. A very important point, sometimes overlooked, is the concentration of the sample used in the test. Neuromuscular transmission in the patient with myasthenia gravis usually operates with reduced safety margin rather than being blocked completely. Hence one may suppose that any blocking agent in the patients' blood and extracellular fluid will be present at an average concentration which is subliminal with respect to complete interruption of neuromuscular transmission. If the test preparation

has junctional characteristics such as those in man, and if in the assay procedure one measures only the muscle tension in a neurally initiated twitch or brief tetanus, then diluting the serum sample before applying it to the test preparation will make detection of the hypothetical blocking agent difficult or impossible. The critical question of assay sensitivity is clearly illustrated in a different way by the studies of Bergh [*1*] who showed that d-tubocurarine, even though present in the blood of man and animals in a concentration sufficient to cause respiratory paralysis, could barely be detected by a bioassay method utilizing cat tibialis anticus muscle to which serum samples were applied via close intraarterial injection.

Another important factor in assay of an unknown neuromuscular blocking agent is the question of its time course of action. The neuromuscular blocking agent, botulinum toxin, has a latency of twenty to thirty minutes before it becomes effective [*8,9*]. Similar latency might also be a factor in any serum assay and it might be necessary, therefore, to maintain an effective concentration at the target site for many minutes or even longer in order to allow for slow penetration and other unknown factors. During this time it might be necessary to apply fresh sample material in order to overcome possible simultaneous inactivation.

From the foregoing line of reasoning we conclude that experiments in which negative results were obtained following injection of small volumes of serum from myasthenic subjects into whole animals [*10*] may be discounted on the grounds that concentration and time factors were unfavorable.

Although amphibian sartorius muscle is a convenient test preparation from many points of view, the fact that each muscle fiber has at least two neuromuscular junctions might make it more difficult to depress a neurally initiated twitch or tetanus following topical application of blocking agents, particularly those of low penetrating power. For this and other reasons we now believe that the use of muscle tension recording as an end-point in the assay of neuromuscular blocking agents is a relatively crude technic. It might be better to perfuse single endplates with serum while using an intracellular microelectrode to record muscle fiber transmembrane potentials at this zone. Then, after an adequate perfusion, the motor nerve could be stimulated and the resulting changes in transmembrane potential recorded. Comparison with results obtained using control subjects should give a sensitive indication of the presence of a neuromuscular blocking agent and, in addition, this analysis could provide clues as to the locus of action. We intend to pursue this course in a future study.

In the light of the preceding discussion it is worthwhile to re-examine the work of Wilson and Stoner [*2*]. In correspondence and conversation Wilson has kindly provided us with additional information not found in the paper.

These authors stated that 1 ml. of serum was added to a bath containing a frog sartorius muscle-motor nerve preparation. Wilson believes that the bath capacity was 10 to 15 ml. Thus his solution contained 6 to 9 per cent serum, a rather low concentration. The stimulus intensity was originally described by Wilson and Stoner as just submaximal. In retrospect, Wilson regards this as a poor choice. With this we agree on the ground that a just maximal stimulus would no longer stimulate all motor axons if for any reason the excitability of each axon in the population decreased slightly.

Wilson and Stoner stated that eleven of thirteen myasthenic serums gave a depression in muscle tetanus tension varying from 10 to 100 per cent. These data apply to the maximum amplitude of the muscle tetanus tension recorded at the end of 140 minutes immersion in serum-Ringer solution mixture. No rate of development is given but it is stated that the depression appears after eight minutes latency. Wilson no longer possesses data on the individual experiments which might be examined in tabular form. His recollection is that for the eleven positive results the loss of tetanus tension *averaged* 20 to 25 per cent of the control value. Evidently, many of the samples tested by them produced a moderate reduction of tetanus tension.

Our results can hardly be described as a resounding confirmation of those obtained by Wilson and Stoner. We have been able to demonstrate serum activity with three of the twelve patients listed in Table IIA and for these three cases the reduction in maximum tetanus tension measured after forty minutes exposure to serum-Ringer solution averaged 23 per cent, which may be compared with a 5 per cent reduction for the control subjects. In the second set of experiments (Table III), in which we believe the assay conditions were more favorable than those of Wilson and Stoner, one of six

samples showed activity. In the final set of experiments (Table IV), which included a previously used and therefore selected sample, two of the five serums were active. We note that Struppler [*3*] remarks on the difficulty of obtaining consistent muscle tension depression when he uses the phrenic nerve-diaphragm preparation in the *in vitro* assay of serum from myasthenic subjects.

Discussion and Significance of Our Results. The data shown in Table IIA bring out the unexpected twitch augmentation effect which occurred with several samples from myasthenic patients but with none of the samples from control subjects in this series. At first we supposed that the augmented single "twitches" were in reality brief tetanic contractures produced via initiation at the endplate of not one but a burst of several muscle action potentials. This could be an effect caused by anticholinesterase drug still persisting in the patients' blood because the presampling drug withdrawal period was too short. While this explanation [*11*] cannot be completely ruled out, we have reasons for doubting its sufficiency. The twitch augmentation produced by MG4-S1-AE and MG6-S1-AE samples (Table IIA) was continually maintained without decrement for sixty minutes when control plasma-Ringer solution was used to replace the mixture which contained plasma from a myasthenic patient. Also (Table IIA) the MG5-S1-AE sample caused twitch augmentation although this plasma could contain no anticholinesterase because the patient was receiving no such medication at the time. Furthermore, under other conditions as shown in Table IV, twitch augmentation could be produced by serum from normal control subjects.

We have therefore considered other reasonable explanations of the twitch augmentation effect. It might, for example, result from the relative hypertonicity of our plasma or serum-Ringer solution mixtures, the osmotic pressure of human serum being 28 per cent greater than that of the frog [*12*]. It is known that the frequency of the quantal discharges from motor nerve terminals is greatly increased by a rise in osmotic pressure [*13,14*] and this might conceivably facilitate neuromuscular transmission. We have not performed the simple control experiment to test this line of reasoning, but even in the absence of such information it would seem that the argument is faulty because many serum samples from normal subjects essentially equally hypertonic with those just mentioned did not cause augmentation of the single twitch. (Tables IIA and IV.)

Another attractive explanation for twitch augmentation (for which, however, we have no decisive evidence) is that serum from certain subjects possesses some agent which increases the duration of the muscle fiber active state.

The fact that augmentation of the end tetanus tension (Table III) by serum has a short latency and is so well maintained might lead one to suspect that this effect is produced by some easily diffusible constituent of the serum-Ringer solution mixture. Among the ionic constituents, potassium and calcium are likely candidates. After use in the bioassay indicated by the code number (Table III) we obtained potassium ion concentrations* for the following serum-Ringer solution mixtures.

	K^+
MG2-S2-AE	4.0 mEq./L.
MG16-S1-AE	3.4 mEq./L.
MG19-S1-AE	3.9 mEq./L.
MG19-S2-NE	3.8 mEq./L.
C4-S2-NE repeat	3.6 mEq./L.

Since the Ringer solution we used contained 2.5 mEq./L. potassium, the nerve-muscle preparation during these tests was subjected to an increase in extracellular potassium ranging from 0.9 to 1.5 mEq./L. This rise might account for the end tetanus tension augmentation but control experiments are required before such an explanation can be accepted.

In retrospect we realize that Ca^{++} ion determinations on all samples might have been valuable but unfortunately they were not carried out at the time of this study.

One may now consider the results obtained with samples which caused depression of the muscle tension. The data listed in Table IIA are in chronological order, and the first three tests of this series (MG1-S1, MG2-S1, MG3-S1) show a depression of the tetanus tension at the forty minute point. These experiments, which were begun in August, were resumed in October of the same year and the next test on MG3, using a fresh sample drawn seventy days later, gave no significant tension depression. To our chagrin this was true for all subsequent samples in this series which were obtained from other patients. It is possible that the relatively high

* Courtesy Dr. Charles Pallavicini, Department of Physiology, Columbia University.

bath temperature (27 to 28°C.) in the first three assays might have enhanced the tetanus depression effect of the serum. However, this argument is weakened by lack of significant tension depression in four other myasthenic sample assays (and two control samples), all of which were conducted at 27 to 29°C.

With respect to the effect of plasma and serum from myasthenic patients on the peak tetanus tension, we have shown in Table III that a reduction was obtained in four tests of MG19-S1 and a single test of MG19-S2. As stated earlier, the irreversible depressant action of these serums did not parallel that produced by d-tubocurarine. The cytolytic action shown by MG14-S2-NE and MG19-S2-NE on muscle fibers appeared to be an adequate basis for explaining the irreversible depression of peak tetanus tension. If these serums contained membrane-destroying components it is not difficult to assume that under some conditions they might, without causing dissolution, produce important physiological changes in muscle cell membranes. However, before we can assign this property to myasthenic serum we must also keep in mind the fact that muscle cell cytolysis was also observed, delayed it is true to the recovery period in Ringer solution, following application of one control serum C7-S1. Furthermore, in experiments not reported here, single endplates have been perfused using other samples of normal human serum, diluted with water to make them isotonic with frog plasma. Two of these relatively concentrated samples produced muscle cell cytolysis with a latency of seven to thirteen minutes. Aliquots of these two samples consistently produced cytolysis in several fresh nerve-muscle preparations, showing that the effect cannot be the consequence of some uncommon pecularity of a particular frog muscle. On the other hand, in these experiments other serum samples from control subjects did not produce any morphological changes, nor did they alter membrane behavior as judged by intracellular recording of the transmembrane potential during perfusion. We therefore conclude tentatively that serum obtained from certain patients with myasthenia gravis possesses in higher degree, a cytolytic activity, which is also shown on occasion by serum from apparently normal persons. Clearly, the cytolytic action shown by certain serums from myasthenic patients needs to be more carefully explored. For this reason we intend to employ two experimental tests in making a wider survey of the serum cytolytic activity in both normal and myasthenic subjects. We are hopeful that the results may provide a simple test of diagnostic value and, in addition perhaps, evidence of more fundamental significance.

Finally one may consider whether or not there is any relation between the results of our assays and the "clinical status" of the patient. By "clinical status" we mean at least a rough quantitation of the over-all intensity and activity of the disease process based on clinical information concerning the patient. The difficulties and pitfalls inherent in such an assessment are evident. In Table I we have attempted to provide a list of certain items describing our patients which we believe might be useful in a search for clinical correlation.

As was noted earlier in this paper, augmentation of the single twitch and the end tetanus tension was produced by plasma and serum samples from both myasthenic and normal persons. We find no clear relationship between the magnitude of the augmentation and either the trend of the disease severity or the distribution of disease symptoms in the body. The augmentation effect is exhibited more frequently by samples from myasthenic subjects than by samples from control subjects, but the significance of this difference cannot be established at present.

With respect to depression of muscle tension, our data show positive results for MG3-S1, MG14-S1, MG19-S1, MG19-S2 and to a lesser extent for MG1-S1 and MG2-S1. These results are in no clear relationship with the information listed in Table I.

Circulating Inhibitor Hypothesis. It is now appropriate to raise once more the question of whether or not a circulating neuromuscular blocking agent is present in the blood of the myasthenic patient. Our series of twenty-two patients provided relatively few plasma or serum samples which caused muscle tension depression. They were MG1-S1, MG2-S1, MG3-S1, MG14-S1, MG19-S1 and MG19-S2. One may make the assumptions (1) that symptoms of neuromuscular transmission deficit can exist only if the inhibiting agent is present at the affected junctional sites, (2) that if such an agent is present at neuromuscular junctions it must also appear in the blood in liminal or supraliminal concentration, and (3) that our assay method is valid. If these assumptions are

accepted, our results could be used as an argument against the circulating inhibitor hypothesis. This argument becomes still stronger if in addition one takes the view that the depressant action shown by certain of our samples is a property occasionally exhibited by samples from non-myasthenic persons.

On the other hand, one may make another reasonable assumption, that the symptoms of neuromuscular deficit can exist in the absence of the agent which originally produced the junctional derangement. In this case the agent might be present and active in the body over relatively short intervals of time. Under these circumstances there would be a much diminished chance of obtaining blood samples showing activity, and hence our results could be considered to be compatible with the circulating inhibitor hypothesis.

At present we do not know of any compelling argument which makes it possible for us to decide between either of these sets of assumptions. Therefore, we do not consider the data in this paper to be crucial in the testing of the hypothesis herein considered.

SUMMARY

1. Plasma and serum samples were obtained from twenty-two patients with myasthenia gravis and nine normal control subjects. Some of the samples were taken after exercise under ischemia.

2. These samples were applied, in various dilutions, to the frog sciatic nerve-sartorius muscle preparation *in vitro*. The twitch and tetanus tensions of the preparation were measured, using indirect stimulation under three different conditions.

3. Samples from five of the myasthenic patients caused a reduction of maximum tetanus tension beyond that produced by those of the control subjects.

4. Samples from thirteen of the myasthenic patients caused appreciable augmentation of the twitch or end tetanus tension. Such augmentation was seen with samples from three of the control subjects. Possible causes of the augmentation effect are discussed.

5. The question of the demonstration of a circulating neuromuscular blocking agent in myasthenia gravis is discussed with reference to: methods of bioassay, results reported in this paper and by other investigators, possible properties of such a blocking agent, and clinical status of the myasthenic patient.

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Plasma Catechol Amine and Electroencephalographic Responses to Acute Postural Change*

Evidence of a Deficient Pressor Amine Response in Postural Hypotension

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THE hemodynamic adjustment to an abrupt change in body position from the horizontal to the vertical has been amply described in the literature [*1–9*]. Assumption of the upright position results in pooling of blood in the extremities and a reduction of the central venous pressure. The attendant fall in venous return results in a diminished cardiac output. This "functional hemorrhage" into the lower part of the body would regularly result in syncope if it were not for compensatory baro-receptor reflexes [*3*]. These reflexes defend against a fall in central aortic pressure and maintain adequate cerebral blood flow. The associated rise in the pulse rate and diastolic pressure may result from a reflex increase in sympathetic tone.

Syncope, as a manifestation of cerebral oligemia, is indicative of a failure of the cardiovascular apparatus to maintain adequate arterial perfusion of the brain. Syncope may be of two types: vasodepressor syncope (the common faint), and that associated with the relatively uncommon disorder of postural hypotension [*1*]. Syncope frequently occurs on tilting normal subjects upright [*2*], and represents a vagotonic reaction superimposed on the normal sympathetic defense against the orthostatic stress [*4*]. The trigger mechanism is obscure, but the development of the signs and symptoms of increased cholinergic nerve activity prior to the fall in blood pressure suggest that it is the primary mechanism in the faint [*1,4*]. Reflex peripheral vasodilatation, as evidenced by a sudden increase in limb flow preceding the faint, is a manifestation of this depressor response [*4*]. The attendant peripheral pooling of blood results in cerebral oligemia and syncope. In contrast, the faint attending postural hypotension is the sequel of apparent failure of a reflex vasoconstriction to compensate for the peripheral pooling of blood and is distinguished by absence of the signs and symptoms of an excess of cholinergic nerve activity [*1,3,10,11*]. The characteristic change on tilting upright a subject with postural hypotension is a prompt, marked and progressive fall in both systolic and diastolic blood pressure with narrowing of the pulse pressure, followed by syncope. In both types of syncope, vasovagal and that attending postural hypotension, a failure of cerebral arterial perfusion pressure has been demonstrated [*7*].

In their original description of postural hypotension in 1925 Bradbury and Eggleston [*10*] concluded that "paralysis of the sympathetic vasoconstrictor endings seems to be the only adequate explanation of the blood pressure reactions observed in these cases." Much of the subsequent work has helped to confirm this conclusion. Ellis and Haynes [*11*] were im-

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pressed by the frequent association of postural hypotension with neurological disease, concluding that in such instances there was an interruption of the reflex sympathetic pathways. Stead and Ebert [*3*] noted that in patients with postural hypotension there was a normal blood volume with the same amount of peripheral pooling as was found in normal subjects. They demonstrated a number of faulty sympathetic responses and concluded that the basic problem was not excess pooling of blood but a failure of reflex control of the arterial pressure in the face of normal pooling.

More recently, measurements of urinary epinephrine and nor-epinephrine have been related to orthostatic phenomena. Sundin [*8*] demonstrated by bioassay a fourfold increase in the rate of urinary excretion of epinephrine and nor-epinephrine on tilting normal subjects upright to 75 degrees. This correlates with an earlier observation [*12*] of an increased output of epinephrine and nor-epinephrine from the cat's adrenal gland following carotid occlusion. A high "G" tolerance in man has also been correlated with a higher nor-epinephrine output in the urine during centrifugation than in subjects with a low "G" tolerance; urinary epinephrine output did not show significant changes of a parallel nature [*13*]. Von Euler et al. [*14*] demonstrated a marked fall in urinary epinephrine excretion without any diminution in urinary nor-epinephrine excretion following bilateral adrenalectomy in man. This supports the concept that most of the urinary epinephrine derives from the adrenals whereas the urinary nor-epinephrine derives from the adrenergic nerve endings. On measuring the twenty-four-hour urinary excretion of epinephrine and nor-epinephrine in two subjects with postural hypotension, Luft and von Euler [*15*] found markedly depressed values for nor-epinephrine and equivocally depressed values for epinephrine. In a series of ten females with bilateral adrenalectomy for metastatic mammary carcinoma [*16*] tilting upright to 75 degrees resulted in a normal increase in urinary nor-epinephrine excretion; urinary epinephrine excretion, however, failed to show a significant rise. These observations suggest that on tilting the rise in urinary nor-epinephrine results primarily from increased reflex adrenergic nerve activity and the rise in urinary epinephrine from reflex stimulation of the adrenal medulla.

The studies reported here explore the possible relationship between these physiological observations and the common clinical problems of dizziness, "blackout" spells and light-headedness. Of twenty-five patients with a variety of disease states, referred to this laboratory for tilt table study because of such symptoms, seven had a history of definite, recurrent syncopal spells. Of these seven two were young males with proved, well compensated congenital aortic stenosis; the third was a subject with bilateral adrenalectomy for malignant hypertension; the fourth was a subject with a bilateral thoracolumbar sympathectomy for severe hypertension; the fifth was a young female with chronic ulcerative colitis in remission in whom the syncopal spells had developed following the administration of iproniazid (Marsilid®) [*17*], the sixth and seventh had no established disease. In addition, four healthy young adults have been studied. Eleven subjects are reported here: the four normal subjects and the seven with recurrent syncopal spells.

METHOD

All subjects were ambulatory and were studied in the early afternoon one to two hours after their usual noon meal. Each was rested in the horizontal, supine position on a standard tilt table with a 1 inch sponge rubber mattress for a period of forty minutes prior to tilting. Electroencephalographic and 1-lead (V_4) electrocardiographic tracings were recorded continuously by a Grass, Model III, apparatus during the control period and after tilting upright to 60 degrees. Six channels of the electroencephalograph were employed: left and right frontal, left and right parietal and left and right occipital, all of which were referred to interconnected ears. The seventh channel was left idle and the eighth was employed for recording the 1-lead (V_4) electrocardiogram. Serial blood pressures were recorded every thirty to sixty seconds from the left arm by auscultation with a standard aneroid blood pressure cuff. An inlying No. 20 needle with stylet was placed in the antecubital vein of the right arm. Both arms of the subjects remained at rest by their sides throughout the study. Venous blood samples were drawn during the control period and two and a half, five, ten, twenty and thirty minutes after tilting upright. Each sample of 15 cc. blood was mixed in a tube of 0.5 cc. aqueous heparin and placed in ice water. The plasma was separated from these blood samples by centrifugation and stored at $-18°$c. Subsequent analysis of the epinephrine and nor-epinephrine plasma concentrations was carried out using the Aronow and Howard modification [*18*] of the Weil-Halherbe and Bone method [*19*]. It has been shown that this fluorometric determination of ethyl-

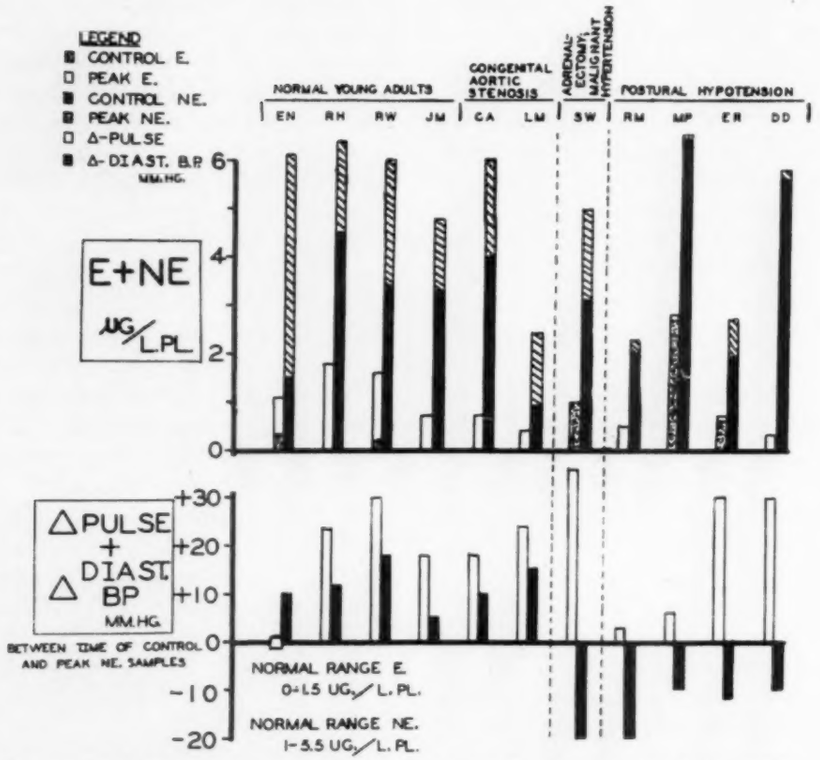


FIG. 1. Control of peak post-tilt epinephrine (E.) and nor-epinephrine (NE.) plasma concentrations with pulse rate and diastolic blood pressure changes of individual subjects tilted.

enediamine condensation products is not specific for epinephrine and nor-epinephrine but measures other hydroxphenol compounds in the plasma, notably, 3,4-dihydroxphenyl-acetic acid (dopac) [*20–22*]. However, the results to be reported are concerned with acute changes in the labile hormonal fraction and not absolute levels. Therefore, for practical purposes the levels are reported as representative of the epinephrine and nor-epinephrine plasma concentrations. In this laboratory the normal range for epinephrine is 0 to 1.5 μg./L. plasma and for nor-epinephrine, 1.0 to 5.5 μg./L. plasma.

RESULTS

Four of the subjects with a history of syncopal spells (including the patient with a sympathectomy and the patient receiving iproniazid therapy) had a blood pressure response characteristic of postural hypotension (subjects R. M., M. P., E. R. and D. D., Table I), as defined in the introduction. The findings in this distinctly pathological group are compared with the findings in the other seven subjects. Figure 1 is a graphic representation of data from Table I to demonstrate the relationship between the catechol amine and hemodynamic changes on tilting. Figure 2 is a graphic representation of data from Table II, comparing the difference in the averages for the response of blood pressure and catechol amine levels between the four subjects with postural hypotension and the others (excluding the patient with an adrenalectomy).

Hemodynamic Response. Of primary importance was the relationship between the hemodynamic response and the change in catechol amine levels, particularly the nor-epinephrine level. Therefore, the systolic and diastolic blood pressure and heart rate, recorded precisely at the time of drawing the last control blood sample prior to the tilting, are compared with the systolic and diastolic blood pressure and heart rate recorded precisely at the time of drawing the blood sample which proved to have the peak level in nor-epinephrine concentration following the tilt; the latter ranged from two and a half to twenty minutes after the tilt. These two points in the study are referred to subsequently as "the two reference times." The four normal subjects and the two subjects with well compensated congenital aortic stenosis are considered together as a control group, and are

TABLE 1

HEMODYNAMICS, CATECHOL AMINE AND ELECTROENCEPHALOGRAPHIC DATA ON THE CONTROL SUBJECTS AND SUBJECTS WITH POSTURAL HYPOTENSION

Patient	Age (yr.)	Sex	Diagnosis	History of Syncopal Spells	Blood Pressure (mm. Hg)						Heart Rate			Epinephrine μg./L. plasma (venous)				Nor-epinephrine μg./L. plasma (venous)				Electroencephalographic Changes Post Tilt	Response to Tilt
					Systolic			Diastolic															
					Control*	Post Tilt†	Change	Control*	Post Tilt†	Change	Control*	Post Tilt†	Change	Control‡	Maximum Level Post Tilt	Change	Minutes After Tilt to Time of Level	Control‡	Maximum Level Post Tilt	Change	Minutes After Tilt to Time of Maximum Level		
E. N	31	F	Normal subject	0	120	130	+10	70	80	+10	78	78	0	.3	1.1	0.8	5′	1.6	6.1	4.5	5′	None	.....
R. H.	31	M	Normal subject	0	118	104	−14	78	90	+12	84	108	+24	0	1.8	1.8	20′	4.5	6.3	1.8	20′	None	.....
R. W.	34	M	Normal subject	0	128	112	−16	82	100	+18	72	102	+30	0.2	1.6	1.4	10′	3.4	6.0	2.6	10′	None	Vasovagal faint
J. M.	29	M	Normal subject	0	120	115	−5	80	85	+5	72	90	+18	0	0.7	0.7	5′	3.3	4.8	1.5	2.5′	None	Vasovagal faint
C. A.	15	M	Congenital aortic stenosis	+	100	100§	0	70	§80	+10	60	§78	+18	0	0.8	0.8	5′	4.0	6.0	2.0	5′	Diffuse slowing at time of syncope	Vasovagal faint
L. M.	26	M	Congenital aortic stenosis	+	100	95	−5	65	80	+15	60	84	+24	0	0.4	0.4	2.5′	0.9	2.4	1.5	5′	None	Vasovagal faint
S. W.	61	M	Post adrenalectomy for malignant hypertension	+	270	160	−110	140	120	−20	72	108	+36	0.8	0	0	.....	3.1	5.0	1.9	20′	Left parietal slowing at time of maximum fall in blood pressure	.....
R. M.	56	F	Postural hypotension	+	170	80	−90	95	75	−20	84	87	+3	0	0.5	0.5	10′	2.0	2.3	0.3	10′	None	Marked hypotension; no faint
M. P.	73	F	Postural hypotension	+	140	108	−32	74	64	−10	66	72	+6	2.7	2.8	0.1	5′	6.4	6.5	0.1	2.5′	None	Marked hypotension; no faint
E. R.	57	M	Postural hypotension (post sympathectomy for hypertension)	+	220	138	−82	136	124	−12	60	90	+30	0.6	0.7	0.1	.....	1.9	2.7	0.8	2.5′	Parietal and occipital slowing at time of maximum fall in blood pressure	Marked hypotension; syncope
D. D.	30	F	Postural hypotension (chronic ulcerative colitis; iproniazid therapy)	+	75	50	−25	45	35	−10	72	102	+30	0	0.3	0.3	2.5′	5.6	5.8	0.2	5′	Diffuse slowing at time of maximum fall in blood pressure	Marked hypotension; no faint

* Level at time of drawing control blood sample for catechol determination prior to tilt.

† Level at time of drawing blood sample at point of peak nor-epinephrine response after tilt.

‡ When more than one control blood sample drawn, the last one just prior to tilt recorded.

§ Peak value for pulse and blood pressure taken prior to peak nor-epinephrine, as subject fainted at time of peak nor-epinephrine with unobtainable blood pressure

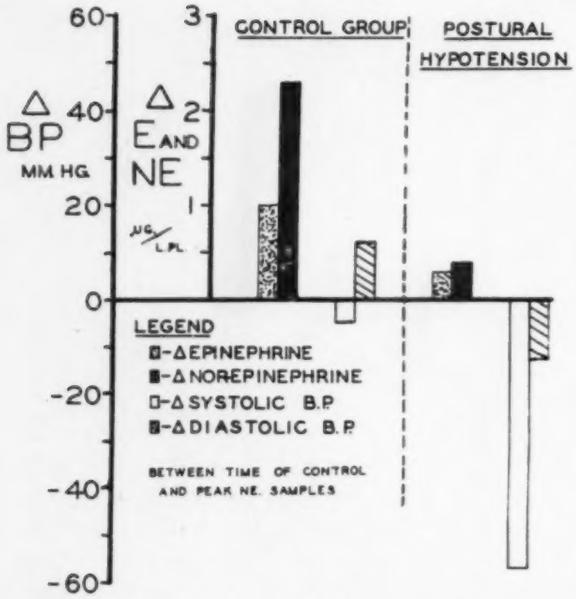


FIG. 2. The average increments in epinephrine (E.) and nor-epinephrine (NE.) plasma concentration and the average change in systolic and diastolic blood pressure on tilting in the control group (four normal subjects and two with congenital aortic stenosis) and the corresponding average changes in the group with postural hypotension.

TABLE II
MEAN CHANGES IN CATECHOL AMINES AND BLOOD PRESSURE ON TILTING

Data	Control Group	Group with Postural Hypotension
No. cases	6	4
E—μg./L. plasma (venous), average rise after tilt	1.0	0.3
NE—μg./L. plasma (venous), average rise after tilt	2.3	0.4
Systolic blood pressure, mm. Hg, average change on tilt*	−5	−57
Diastolic blood pressure, mm. Hg, average change on tilt*	+12	−13

* Change between time of drawing control blood nor-epinephrine and peak blood nor-epinephrine sample after tilting.

contrasted with the subject with an adrenalectomy for malignant hypertension and the four subjects with postural hypotension. In this control group the *systolic pressure* rose 10 mm. Hg in one subject, remained unchanged in another, and fell in the other four subjects between the two reference times indicated, with an average fall of 5 mm. Hg (range −16 to +10). This corresponds to an average fall of 4 mm. Hg in ninety-one normal subjects after three minutes of tilting to 70 degrees reported by Allen et al. [2]. The four subjects with postural hypotension all had prompt and progressive falls in systolic blood pressure, averaging 57 mm. Hg (range 32 to 90) between the two reference times.

The *diastolic pressure* rose in all six control subjects, averaging 12 mm. Hg (range 5 to 18) between the two lines. This corresponds to an average rise of 5 mm. Hg in the large series of Allen et al. [2]. The four subjects with postural hypotension had prompt and progressive falls in diastolic pressure, averaging 13 mm. Hg (range −10 to −20) between the two reference times. The subject with adrenalectomy had a marked and immediate fall in the systolic (110 mm. Hg) and diastolic (20 mm. Hg) pressure, as found in the group with postural hypotension. However, following this initial fall, there was a sharp secondary rise in the systolic and diastolic pressure. In contrast, the systolic and diastolic pressure in the group with postural hypotension fell promptly and progressively without any secondary rise. This is the characteristic feature of this syndrome as defined by others [3,10,11].

The *heart rate* rose in all but one of the subjects in the control group. The average rise was 19 beats per minute (range 0 to 30). Allen et al. [2] found an average rise of 15. The subject with adrenalectomy had a rise of 36 beats per minute. Two of the four subjects with postural hypotension had insignificant rises in rate despite marked hypotension (3 and 6 beats per minute, respectively); the other two each had a large rise of 30 beats per minute in association with marked hypotension. This corresponds with the finding of Ellis and Haynes [11] who noted that an unchanging heart rate despite an orthostatic stress is a common but not invariable feature of postural hypotension.

Syncope occurred in two of the four normal young adults after seven and twenty minutes of tilt, respectively. The over-all incidence of syncope on the tilt table was 20 per cent in a series of 111 healthy, young men reported by Allen et al. [2]. Both young men with congenital aortic stenosis fainted after three and a half and six minutes, respectively. The syncope in these four subjects was of the vasodepressor variety, with the usual prodromes of pallor, sweating, restlessness, and sighing respirations. The vagotonic reaction was superimposed after a

TABLE III
A COMPARISON OF CATECHOL AMINE RESPONSE ON TILTING AND REMAINING SUPINE

Patient	Study	Plasma Catechol Amines* (μg./L. plasma)								
		Control	Serial Samples for 30 Minutes							
R. W.	No. 1 (Tilt)	E	0.2	0.2	0	0.7	1.6	1.0	0.2	
		NE	3.4	3.4	2.9	3.3	6.0	3.7	3.4	
	No. 2 (Supine throughout)	E	...	0.3	0	0	0	0	0	
		NE	...	3.9	4.2	3.8	3.4	3.1	3.3	
R. H.	No. 1 (Tilt)	E	...	0	1.2	0.5	0.8	0.7	1.8	
		NE	...	4.5	3.4	4.1	3.5	3.4	6.3	
	No. 2 (Supine throughout)	E	...	0	0	0	0	0	0	
		NE	...	2.0	2.3	2.3	2.5	1.8	1.7	

*E = Epinephrine NE = Nor-epinephrine

variable period of time on a normal hemodynamic response to the orthostatic stress and was clearly substantiated by a sudden bradycardia occurring just before or at the time when the blood pressure suddenly fell to levels unobtainable by auscultation. There is nothing in the hemodynamic data preceding the faint to distinguish these subjects from those who do not faint, and the mechanism that triggers the reaction is still unknown. Carotid sinus hypersensitivity could not be demonstrated in those subjects.

The four subjects with a blood pressure response characteristic of postural hypotension all had gradual and progressive falls in blood pressure to a point where it became barely obtainable on auscultation. The danger of syncope was obviated by return to the horizontal position at this point; in E. R. syncope actually did occur just prior to return to the horizontal position. In contrast to the four cases of vasovagal syncope previously described, there was a distinct *absence* of the signs and symptoms of excess autonomic activity, despite the severe hypotension.

Blood Catechol Amine Response. In the four normal subjects and the two with congenital aortic stenosis the venous epinephrine level rose in all instances following the tilt: average rise of 1 μg./L. plasma (range 0.4 to 1.8) after two and a half to twenty minutes. The mean control level was 0.083 ± 0.133 and the mean peak level was 1.067 ± 0.543. The difference of the means is significant ($P < 0.01$). The subject with adrenalectomy had no rise in epinephrine concentration. In the four subjects with postural hypotension the venous epinephrine level showed an average rise following the tilt of 0.2 μg./L. plasma (range 0 to 0.5). The mean control level was 0.850 ± 1.274 and the mean peak level was 1.075 ± 1.161. The difference of the means is not significant ($P > 0.7$).

In the four normal subjects and the two with congenital aortic stenosis the venous nor-epinephrine level rose in all instances following the tilt; average rise of 2.3 μg./L. plasma (range 1.5 to 4.5) after two and a half to twenty minutes. The mean control level was 2.950 ± 1.403 and the mean peak level was 5.267 ± 1.501. The difference of the means is significant ($P < 0.02$). The subject with adrenalectomy had a rise of 1.9 μg./L. plasma in nor-epinephrine concentration. In the four subjects with postural hypotension the venous nor-epinephrine level showed an average rise following the tilt of 0.4 μg./L. plasma (range 0.1 to 0.8). The mean control level was 3.975 ± 2.361 and the mean peak level was 4.325 ± 2.132. The difference of the means is not significant ($P > 0.8$).

In the control group a significant rise in epinephrine and nor-epinephrine concentration correlated with a significant rise in diastolic pressure and an adequate defense of the systolic pressure (average fall of only 5 mm. Hg). In the group with postural hypotension an insignificant change in epinephrine and nor-epinephrine concentration correlated with a significant fall in both the systolic and diastolic pressure. (Table II, Fig. 2.) Syncope, which occurred in four of the control subjects, could not be related to a deficiency in the catechol amine response, as the catechol amines rose to a significant peak just prior to the faint in three cases and at the time of faint in the fourth case. This response was not distinguishable from that of the two control subjects who did not faint.

In order to determine the effect on the catechol amine response of other factors exclusive of the actual tilt stress, in two of the normal control subjects (R. W. and R. H.) the entire procedure was repeated at a later date without the actual tilting. In each instance a forty minute rest period in the supine position preceded the sampling of blood for epinephrine and nor-epinephrine determination. The results are given in Table III and are shown graphically in Figure 3. It can be seen that in both subjects a pronounced rise in the epinephrine and nor-epinephrine concentration followed the tilt

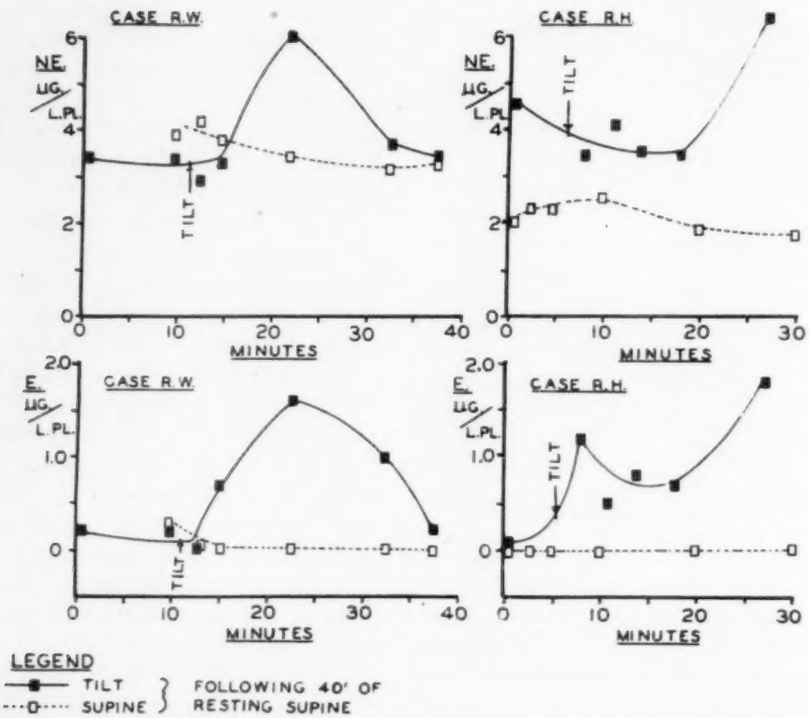


FIG. 3. Comparison of plasma epinephrine (E.) and nor-epinephrine (NE.) concentrations on tilting two of the normal subjects (black squares) with the same subjects at a later date excluding the tilt stress (white squares).

stress but failed to occur when the procedure was repeated, excluding the actual tilting.

Electroencephalographic Changes. The electroencephalogram was normal in all instances during the control period. The alpha activity usually disappeared during the tilting upright and quickly reappeared after reaching the upright position. In one of the subjects with congenital aortic stenosis frontal slowing developed, at the time of syncope, spreading to the parietal and occipital leads, which disappeared promptly on returning the subject to the horizontal position (C. A., Fig. 4). In the subject with adrenalectomy (S. W., Fig. 5) transient left parietal slowing developed at the point of maximum hypotension following tilting, which was of particular interest in view of his history of a transient right hemiparesis. In the subject with a sympathectomy and postural hypotension bilateral parietal and occipital slowing developed, more pronounced on the left after four minutes of tilt at the time of maximum hypotension. This correlated with his history of weakness in the right leg and right-sided visual difficulties following sympathectomy. Furthermore, left carotid insufficiency was demonstrated by the development of involuntary movement of the right arm spreading to the left, following digital compression of the right carotid artery. Finally, in the young female subject with the onset of postural hypotension following iproniazid therapy marked slowing developed in all leads after nine minutes of tilting when her pressure had fallen to its lowest point of 40/30 mm. Hg. (D. D., Fig. 6). This disappeared promptly upon return to the horizontal position.

Hypotension following tilting tended to bring out localized electroencephalographic slowing in the leads overlying a cerebral area when the medical history suggested that the circulation was compromised by pre-existing focal cerebrovascular disease. Such hypotension occasionally brought out diffuse slowing as a manifestation of fainting in the absence of cerebrovascular disease. Some clinical and experimental observations presented by others are corroborative of these phenomena [*23,24*].

The development of an undulating base line of the electroencephalographic tracings due to an increased rate of perspiration underlying the electrocephalographic leads preceded vaso-

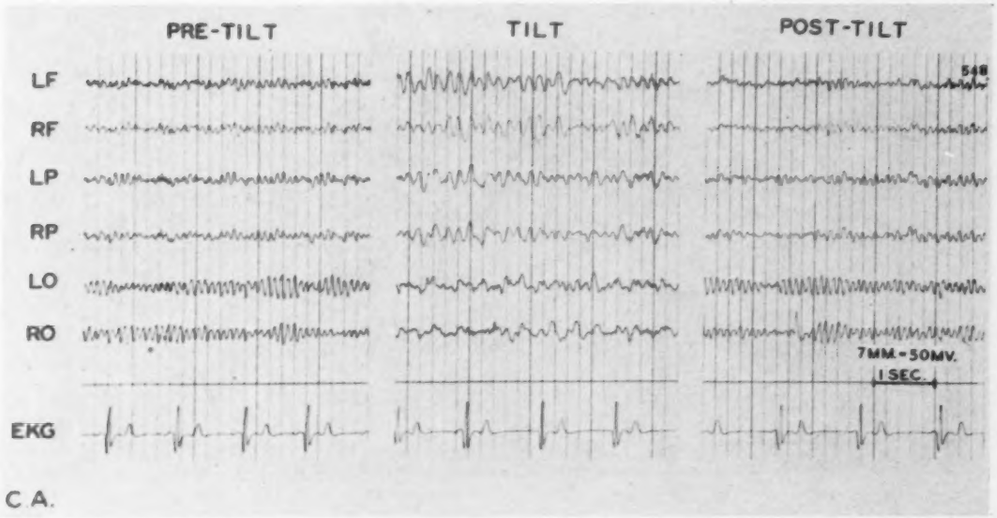


FIG. 4. Electroencephalographic tracings of diffuse slowing in C. A. with congenital aortic stenosis at the time of vasovagal faint after tilting. Slowing disappears promptly on restoration of the blood pressure with return of subject to the horizontal position.

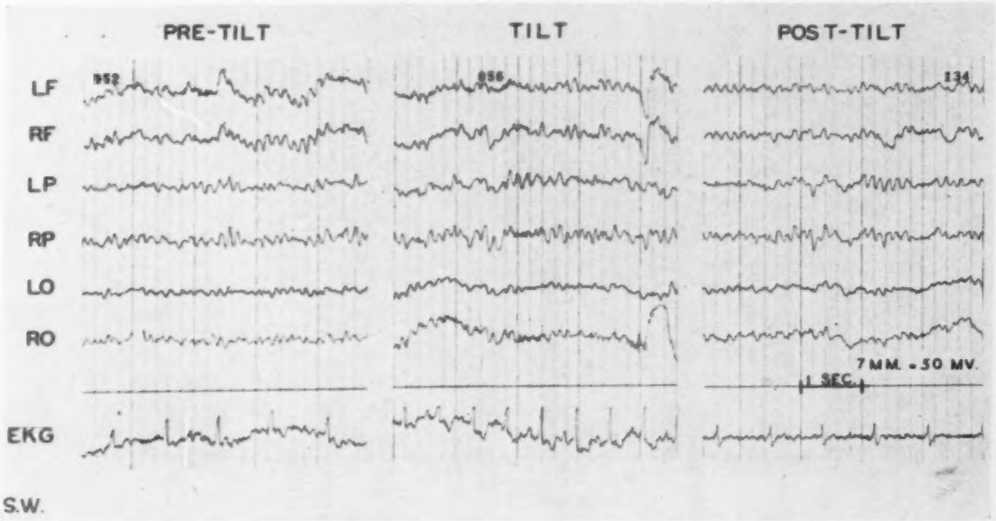


FIG. 5. Electroencephalographic tracings of transient slowing of the left parietal lead in S. W. (postadrenalectomy for malignant hypertension) occurring after tilting at the time of maximum hypotension.

depressor fainting by as much as three minutes. This electroencephalographic artifact, then, may offer the earliest indication of an impending vasovagal faint. Apparently in such syncopal reactions the parasympathetic discharge builds up gradually over minutes rather than occurring suddenly.

Examples of different case studies are shown in Figures 7 to 10. Figure 7 shows the early rise of the nor-epinephrine concentration following tilting in E. N. (normal female); Figure 8 shows the late rise in R. H. (normal male). Figure 9 shows the vasovagal faint in C. A. (congenital aortic stenosis); the maximum rise of the nor-epinephrine concentration occurred at the time of syncope while a marked bradycardia preceded the faint. In the other instances of syncope in the control group the catechol amines reached their maximum level prior to syncope. Figure 10 shows the abnormal response in R. M. with postural hypotension; there was a prompt and progressive fall in the systolic and diastolic pressure with only a slight increase in pulse rate. The latter actually had returned to the control level

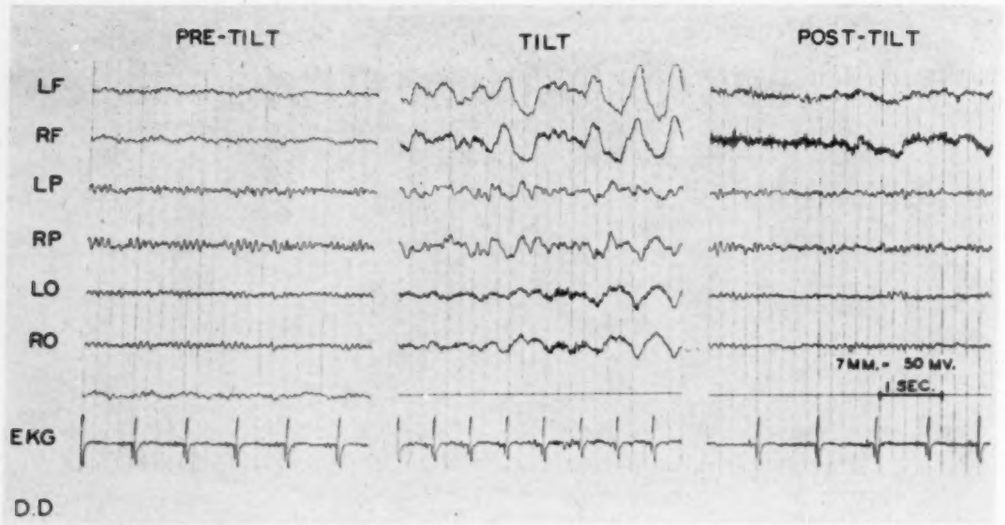


FIG. 6. The diffuse slowing of the electroencephalogram in D. D. with postural hypotension at the time of maximum hypotension following the tilt. Slowing disappears promptly on restoration of the blood pressure with return of the subject to the horizontal position.

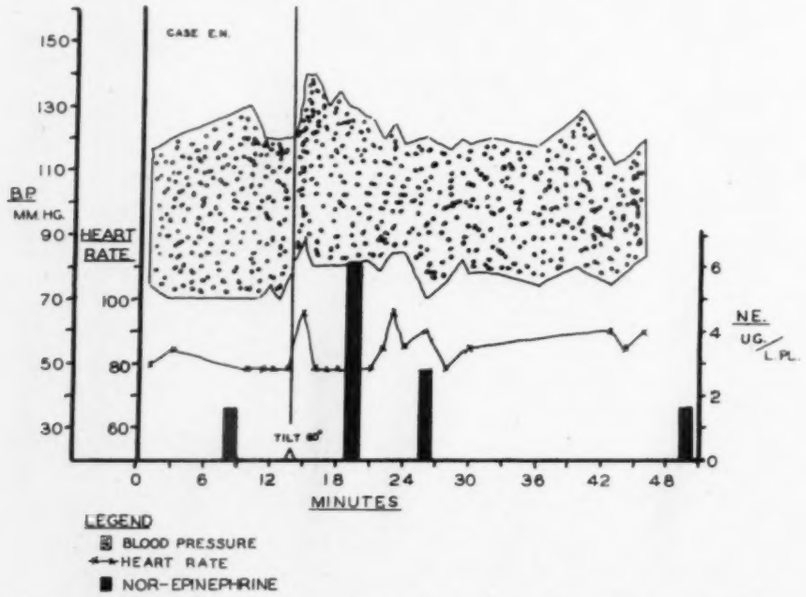


FIG. 7. Study of normal subject E. N., showing early rise in plasma nor-epinephrine (NE.) concentration following the tilt, associated with sustained rise in diastolic and transient rise in systolic blood pressure.

at the time the pressure became virtually unobtainable on auscultation. There was no significant rise in the catechol amine levels.

COMMENTS

Serial measurements of changes in the plasma concentration of the catechol amines give information regarding the temporal relationship between the orthostatic stress and catechol amine release into the circulation. In these studies the rise in diastolic pressure preceded the peak rise in plasma nor-epinephrine concentration by two and a half to twenty minutes. This may result from a time lag between the release of this pressor amine at the effector site in the vessels and its diffusion into the blood stream.

An important consideration is the effect of changes in the arm blood flow on the venous concentration of nor-epinephrine, independent of any change in the rate of elaboration of the

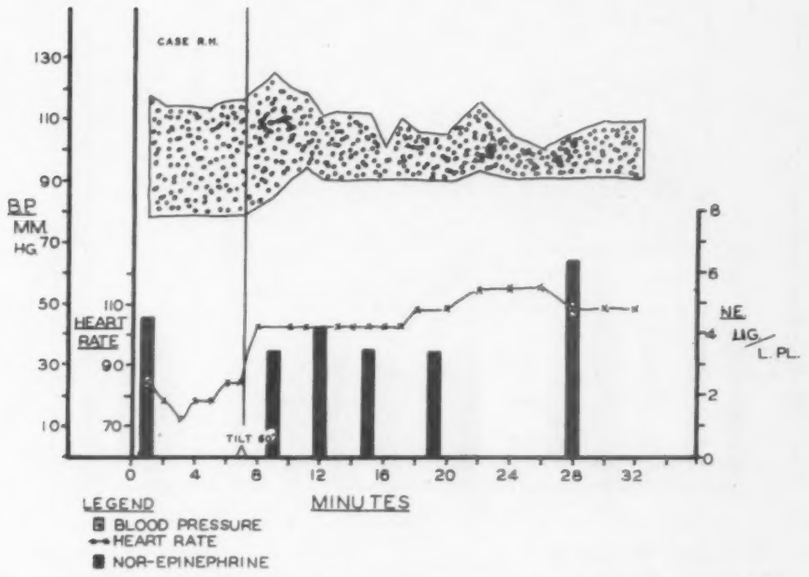


FIG. 8. Study of normal subject R. H., showing late rise in plasma nor-epinephrine (NE.) concentration following the tilt, associated with a sustained rise in diastolic blood pressure and pulse rate.

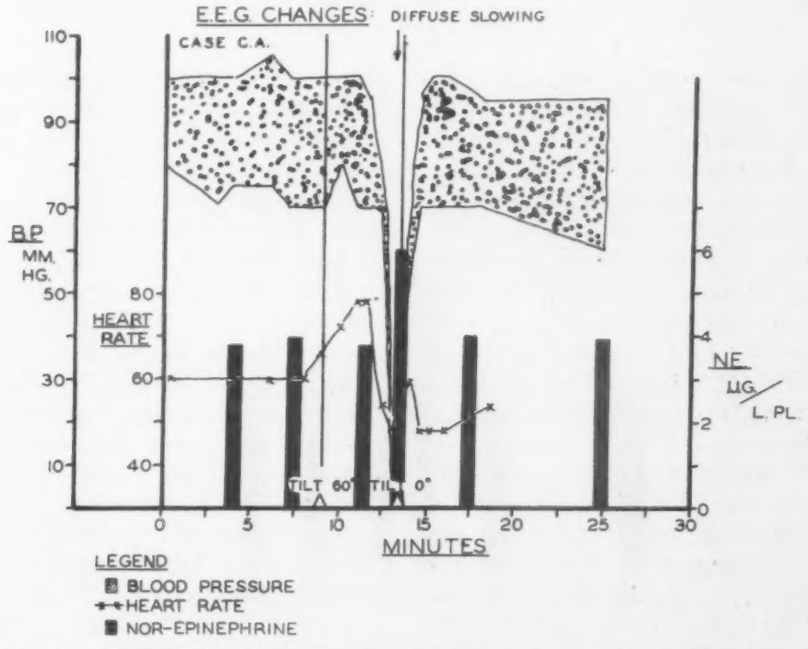


FIG. 9. Study of C. A. with congenital aortic stenosis, showing rise in plasma nor-epinephrine (NE.) concentration at the time of vasovagal faint following the tilt. Bradycardia precedes the fall in blood pressure.

pressor amine. Data from Brigdon et al. [*4*] indicate that the average blood flow after tilting normal subjects upright is in the range of 70 per cent of the control level after the first minute of tilting. This would increase the concentration of nor-epinephrine locally produced in the arm by 30 per cent by virtue of a 30 per cent reduction in the diluting volume of circulating blood in the arm. Garcia et al. [*25*] found in normal subjects at rest that the venous nor-epinephrine concentration averaged 0.36 μg./L. plasma higher than the arterial concentration. If 0.36 μg./L.

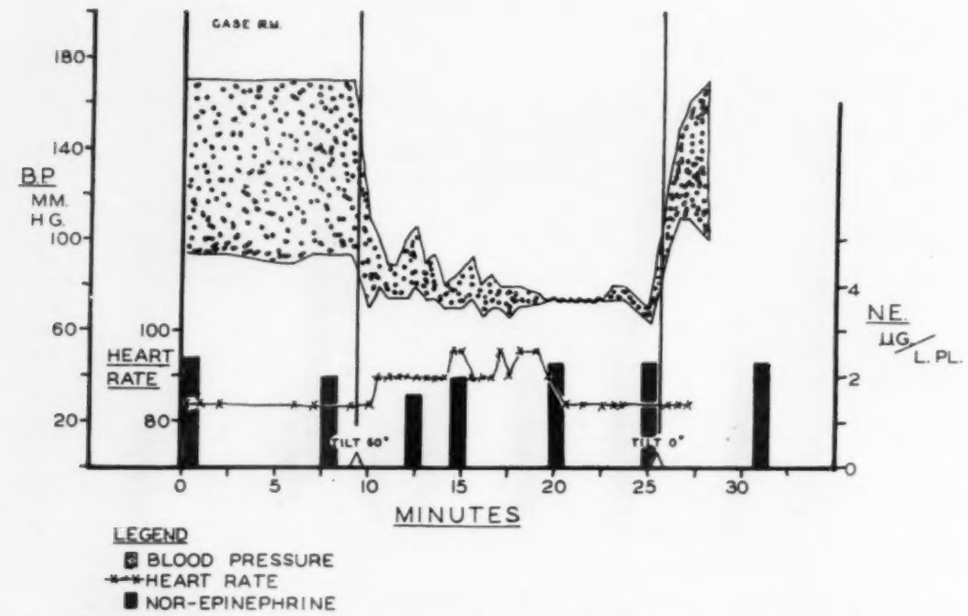


FIG. 10. Study of R. M. with postural hypotension, showing the prompt and progressive fall in systolic and diastolic blood pressure following the tilt with marked narrowing of the pulse pressure.

plasma represents the negative arteriovenous difference, it must represent the amount locally added in the arm at rest. If the rate of elaboration on tilting did not change, the rise in venous concentration due to a 30 per cent reduction in flow would then be 30 per cent of 0.36 µg./L. plasma or 0.11 µg./L. plasma. Since the actual rise in venous concentration on tilting averaged 2.3 µg./L. plasma in the group without postural hypotension, there must have been an appreciable increase in the rate of elaboration (in excess of the rate of destruction), independent of the effect of dilution.

The factor of age must also be considered, since three of the four subjects in the postural hypotension group were over fifty years of age and all the control group were under thirty-five years of age. Experience in this laboratory with the effect of tilting on the venous concentration of the catechol amines in a number of elderly subjects with a variety of disease states has indicated that the older age *per se* does not alter the relationship. These studies will be the subject of another report.

It is notable that two of the subjects with postural hypotension (M. P. and D. D.) had the highest resting levels of nor-epinephrine in the series reported. Whether this represents a truly high level of circulating pressor amine or a relatively large fraction of non-hormonally active fluorescing substrate is uncertain.

Postural hypotension must not be confused with a condition which has been referred to as "orthostatic arterial anemia" [*8,26,27*]. The latter is a condition characterized by a tendency to faint with inordinate falls in systolic pressure and marked rises in pulse rate *without* the development of a fall in diastolic pressure following the assumption of the upright position. In five subjects with this condition Sundin [*8*] found a normal rise in urinary nor-epinephrine excretion on tilting. Maintenance of the diastolic pressure suggests integrity of the pressor amine and peripheral resistance mechanism under an orthostatic stress and distinguishes this condition from postural hypotension. It is not an uncommon response to tilting in the hypertensive patient and was actually noted in one of our two "normals" (R. W., Fig. 11). The epinephrine and nor-epinephrine responses are clearly intact in the face of a fall in systolic pressure of 25 mm. Hg. There was a rise in pulse rate of 30 beats per minute and a rise in diastolic pressure of 15 mm. Hg with a delayed vasovagal faint after twenty minutes of tilt. It has been suggested [*24*] that this condition, of doubtful clinical significance, may actually represent a state of excess sympathetic tone. Poor venous filling of the heart

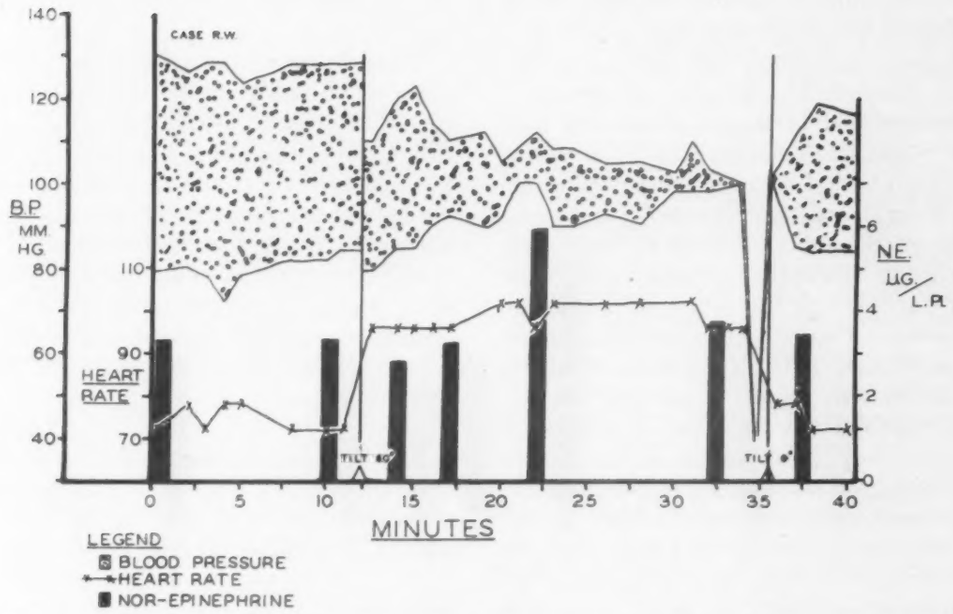


FIG. 11. Study of normal subject R. W., showing response characteristic of "orthostatic arterial anemia," in which tilting resulted in a pronounced fall in systolic blood pressure and rise in pulse rate with *no* associated fall in diastolic blood pressure.

in the presence of normal reflex vasoconstruction could account for such findings.

Of interest is the development of postural hypotension in subject D. D. following iproniazid therapy. Iproniazid has been found to have a tendency to produce postural hypotension when employed as a therapeutic agent in tuberculosis [*17*]. Since the catechol amines on tilting in D. D. did not increase, the effect may be compared with a "pharmacological sympathectomy." The exact level of the block in this reflex release of pressor substance is not known, but the effect suggests a comparison with the known sympatholytic effects of chlorpromazine. There are a number of reports on the development of postural hypotension following the use of chlorpromazine [*28–32*].

The possible effects of emotion at the time of tilting on the reflex release of epinephrine and nor-epinephrine, independent of a physiological release for the hemodynamic defense against a fall in blood pressure, must be considered. Such psychophysiological correlations between emotional stress, vascular responses and catechol amine excretion have been presented by Zuidema et al. [*33*]. It is obviously impossible to distinguish between these psychological and physiological factors. However, a rise in plasma concentration of epinephrine and nor-epinephrine occurred only in conjunction with the physiological stress of tilting upright. When the study was repeated on two of the control subjects excluding the actual tilting, there was no increment in the plasma concentration of these substances (Table III, Fig. 3).

The finding of a significant rise in the venous concentration of epinephrine and nor-epinephrine in the control group and the "flat" response in the group with postural hypotension herein reported suggests that there is a faulty reflex release of these substances in postural hypotension. Postural hypotension developed following sympathectomy in E. R. with a "flat" catechol amine response but did not develop following adrenalectomy in S. W. who had a significant rise in nor-epinephrine and "flat" epinephrine response to tilting. This suggests, further, that it is a failure of a reflex release of nor-epinephrine by the sympathetic nerve endings at the effector site in the vascular bed rather than of adrenal medullary hormones that is the most significant defect in postural hypotension. A deficiency in parasympathetic activity, as well, has been described [*34*] in postural hypotension, consequently a general "autonomic hypofunction" must be considered as characteristic of the condition.

A rise in diastolic pressure and a fall in cardiac

output as simultaneous phenomena on tilting normal subjects [*5*] must mean an appreciable rise in peripheral resistance. The fall in diastolic pressure in postural hypotension on tilting is accompanied by a fall in cardiac output that is of no greater magnitude than that found on tilting normal subjects [*11*]. This would indicate failure of the peripheral resistance to rise. Therefore, the change in diastolic pressure in these two groups on tilting is probably the most convenient parameter for judging the state of arteriolar tone. As shown in Figure 2, the diastolic pressure changes correlated with the nor-epinephrine response in the two groups. This supports the general concept that an acute rise in peripheral arteriolar tone may be followed by a measurable increase in the level of circulating nor-epinephrine. Conversely, a significant increase in the level of circulating nor-epinephrine may be indicative of a rise in peripheral arteriolar tone. A sudden depressor reflex, as in the vasovagal faint, may disrupt this relationship.

SUMMARY AND CONCLUSIONS

A significant rise in the venous concentration of epinephrine and nor-epinephrine was demonstrated in a group of six control subjects in whom the hemodynamic response to tilting upright to 60 degrees was found to be normal.

Four of these subjects (two with congenital aortic stenosis) experienced a vasodepressor type of syncope after three and a half to twenty minutes of tilting, which was superimposed on a normal hemodynamic response and rise in blood catechol amine concentration following this orthostatic stress.

Four other subjects referred for study had a hemodynamic response characteristic of true postural hypotension. In these subjects the venous epinephrine and nor-epinephrine levels failed to show any significant change from the control levels.

Despite falls in blood pressure to levels unobtainable on auscultation in the latter group, there were no signs and symptoms of excess autonomic activity such as were noted in those in the control group who fainted.

Acute changes in the plasma nor-epinephrine concentration correlated well with changes in arteriolar tone, as judged by maintenance of the diastolic pressure level in spite of the tilt stress. Data are presented to support the concept that nor-epinephrine release by the sympathetic nerves is the important factor in this homeostatic mechanism.

When hypotension develops on tilting, localized slow waves may develop in electroencephalographic leads overlying an area in which the circulation has been compromised by focal cerebrovascular disease; diffuse slowing may appear as a manifestation of syncope in the absence of cerebrovascular disease.

Tilting can be a useful clinical diagnostic tool in attempting to understand the large group of undefined syncopal episodes that are so commonly encountered in many medical and neurological clinics.

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Studies of Acute Rheumatic Fever in the Adult*

I. Clinical and Laboratory Manifestations in Thirty Patients

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ACUTE rheumatic fever is generally considered to be a disease of childhood, and the peak incidence of the disease is indeed in the ten to fourteen year old age group. Adults, however, are also susceptible, but the diagnosis of acute rheumatic fever is often more difficult for several reasons: first, because of similarities to other polyarthritides common in adults, such as early rheumatoid arthritis, systemic lupus, gout and the like; second, because such major manifestations as chorea, erythema marginatum and carditis are less frequent in the adult; third, because in the patient with previous rheumatic heart disease the mere presence of heart murmurs, as well as of various non-specific findings such as fever, increased erythrocyte sedimentation rate, the appearance of acute phase reactants and electrocardiographic abnormalities may indicate complications of rheumatic heart disease other than recrudescence of activity. Finally, since acute rheumatic fever is generally considered a childhood disease the physician often fails to consider it seriously in the differential diagnosis in the older age groups.

The purpose of the present study is to describe the manifestations of acute rheumatic fever as they occur specifically in the adult patient, and to discuss the differences and similarities between the disease in the adult and in the child. The questions of proper antibiotic treatment of streptococcal infections and prophylaxis of rheumatic fever in the adult also will be discussed.

MATERIALS AND METHODS

The cases of acute rheumatic fever analyzed in this paper comprise thirty patients at The Mount Sinai Hospital studied in the period 1952 to 1957. A complete history was obtained and physical examinations were performed in each case. Laboratory studies included urinalysis, complete blood count, erythrocyte sedimentation rate (Westergren), determination of C-reactive protein [*1*], antistreptolysin-O titer [*2*], 12-lead electrocardiogram, x-ray films of the chest, throat and blood cultures, and determination of serum proteins. When systemic lupus erythematosus, rheumatoid arthritis or other diseases were considered in the differential diagnosis, appropriate tests including lupus erythematosus cell preparations, sensitized sheep cell agglutination test [*3*], the latex fixation test [*4*] and other tests were performed.

In two of our patients the diagnosis had to await postmortem examination. The other twenty-eight patients fulfilled the criteria recommended by Jones [*5*] but posed additional problems because of the differences between adult and childhood rheumatic fever. In this present series, for example, no patient had chorea, subcutaneous nodules or erythema marginatum—major criteria which are apparently confined to the child. One of the patients who died had "rheumatic pneumonia" suspected clinically and confirmed by postmortem examination.

CLINICAL DATA

Incidence (Table 1). There were twelve males and eighteen females in this series. The age range was from twenty-one to fifty-nine years, with 50 per cent of the patients between the ages of twenty-one and thirty. Seventeen of the patients were of Puerto Rican birth or extraction, five were Negro and eight were white.

Recurrences. Fourteen patients were seen in what appeared to be the initial attack of rheumatic fever, although prior subclinical rheumatic fever could not of course be excluded. The shortest interval between known attacks of acute rheumatic fever was seven months, the longest more than thirty-five years. In ten patients acute attacks developed five or more years fol-

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lowing the preceding episode of acute rheumatic fever. No patient in this series was receiving antibiotic prophylaxis at the time of his recurrent rheumatic fever. Table II demonstrates the variability in the time interval between recurrences.

Associated Disease Including Previously Known Rheumatic Heart Disease. Fourteen of the thirty patients had known rheumatic heart disease prior to the observed episode of acute rheumatic fever. Of these, two had recurrent pulmonary infarctions and one had renal infarction as a complication of their heart disease. The remaining sixteen patients had no knowledge of preceding heart disease. One patient each had hypertension, nephrosclerosis, chronic otitis media, intestinal parasites and previous acute glomerulonephritis.

Preceding Upper Respiratory Infection. Sixty per cent of the patients gave a history of an upper respiratory infection preceding the onset of rheumatic fever. The shortest interval between the respiratory infection and the onset of symptoms of rheumatic fever was one day, the longest four months. (Table III.) Of the eighteen patients with a history of preceding upper respiratory infection, none had received adequate antistreptococcal treatment and eleven had been given no antibiotic therapy at all. Six had received casual injections of penicillin or inadequate amounts of oral penicillin; one patient had taken small doses of erythromycin.

Initial Manifestations. In twenty-eight of the thirty patients the onset of acute rheumatic fever was heralded by symptoms or signs referable to the joints. Arthralgias were the first symptom in 70 per cent, overt arthritis initiated the disease in 20 per cent, and fever and arthralgias were first noted concomitantly in one patient. Of the remaining two patients, one began with cough and the other, who had pericarditis, noted chest pain as the first symptom.

Joints: Involvement of the joints was the most common manifestation of rheumatic fever in this series. Multiple joint involvement of classic migratory character was the rule; in nineteen patients four or more joints were involved, in four patients only two joints were involved, and in five patients three joints were involved. The nature of the joint involvement varied. Arthralgias were a complaint of twenty-eight of the thirty patients. Seventeen per cent of the patients displayed only joint tenderness with or without limitation of motion while another 63 per cent had frank arthritis with heat, swelling and redness. In seven of these latter cases joint effusion was present, confined to the knees. The large joints—knees, ankles, elbows and wrists—were most commonly involved. Table IV depicts the nature and distribution of manifestations referable to the joints.

Murmurs: Twenty-seven of the thirty patients were noted to have some type of cardiac murmur on admission. In twelve, the only murmur present was a soft grade 1 or 2 systolic murmur, usually apical in location and not considered

TABLE I
AGE, SEX AND RACE INCIDENCE OF RHEUMATIC FEVER

	No. of Patients
Age (yr.):	
21–24	7
25–29	8
30–39	9
40–49	4
50–59	2
Sex:	
Male	12
Female	18
Race:	
Puerto Rican	17
Negro	5
White	8

TABLE II
TIME INTERVAL BETWEEN RECURRENCES OF RHEUMATIC FEVER (WHEN KNOWN)

Years Since Previous Attack	No. of Patients
0–2	3
3–4	1
5–6	4
Over 7	6

TABLE III
INTERVAL BETWEEN ONSET OF RESPIRATORY INFECTION (WHEN PRESENT) AND OF RHEUMATIC FEVER

Days	No. of Patients
Less than 7	4
8–14	6
15–28	2
Over 29	6

TABLE IV
NATURE AND DISTRIBUTION OF JOINT MANIFESTATIONS

Joint	Arthralgias	Tenderness and/or Limitation of Motion	Arthritis (heat, swelling, redness)	Effusion
Knees	19	5	13	7
Ankles	14	5	9	..
Wrists	5	3	2	..
Hips	8	3	0	..
Intertarsals	9	2	2	..
Elbows	8	4	1	..
Shoulders	5	4	0	..
Interphalangeals	6	1	4	..
Total no. patients	28	14	19	7

indicative of valvular involvement. The remaining eighteen patients presented with an apical or basal systolic murmur of grade 3 intensity or greater, or with a definite diastolic murmur indicative of valvular disease. Of these, twelve patients had pre-existing rheumatic valvular disease. Mitral valvular murmurs were noted somewhat more frequently than aortic murmurs. Fourteen patients fulfilled the criteria for the diagnosis of acute rheumatic carditis. Of these, five presented with significant murmurs without antecedent valvular disease. Changing murmurs during the course of the illness were noted in seven patients. Six of the remaining nine patients who had pre-existing heart disease showed no change in the character of the heart murmurs; the diagnosis of carditis rested either upon the presence of pericarditis, congestive heart failure appearing for the first time in association with a rheumatic polyarthritis or on the necropsy findings. (Table v.)

Pericarditis: Pericarditis was present in two patients, both of whom had other stigmas of acute carditis. These patients (H. M. and J. S.) had sharp substernal chest pain which was aggravated by inspiration or cough. A pericardial friction rub was present in both. Effusion was demonstrated roentgenographically in one, and the electrocardiogram manifested changes typical of acute pericarditis in both.

Congestive heart failure: Congestive heart failure was noted in eight of the fourteen patients with acute carditis. Dyspnea was a prominent symptom in these patients. Pulmonary rales were noted. A gallop rhythm was present in three patients and one patient had embryocardia. Two patients (I. S. and M. A.) are the subjects of Cases IV and V. In these patients the diagnosis was substantiated at necropsy.

TABLE V
MANIFESTATIONS OF ACUTE CARDITIS IN FOURTEEN PATIENTS

Patient	Age (yr.)	Initial or Recurrent Attack	Pre-existing Heart Disease	Significant Murmur Without Previous RF or Known RHD	Changing Murmurs	Increasing Cardiac Enlargement by X-ray	Pericarditis	Congestive Heart Failure
W. J.	27	I	No	+	+	0	0	0
H. M.	30	R	?	0	+	+	+	+
E. B.	29	R	Yes	0	+	+	0	+
J. S.	21	R	Yes	0	0	0	+	0
J. G.	21	R	Yes	0	0	0	0	+
E. A.	21	R	Yes	0	+	0	0	+
A. O.	36	I	No	+	0	0	0	0
M. Z.	46	I	No	+	+	0	0	0
L. M.*	39	R	Yes	0	0	0	0	+
O. G.†	33	R	Yes	0	0	0	0	+
I. S.‡	48	R	Yes	0	0	+	0	+
J. C.	25	I	No	+	+	0	0	0
M. A.§	30	R	Yes	0	0	0	0	+
P. K.	39	I	No	+	+	0	0	0

* In this patient, congestive heart failure developed in association with rheumatic polyarthritis. With subsidence of the acute rheumatic fever, the congestive heart failure disappeared.

† In this patient, congestive heart failure developed in association with rheumatic polyarthritis. With subsidence of the acute rheumatic fever, the congestive heart failure disappeared and has not recurred for the ensuing three years.

‡ Necropsy findings of acute rheumatic endocarditis and myocarditis.

§ Necropsy findings of acute rheumatic endocarditis, myocarditis and pneumonitis.

P. G. was a twenty-one year old woman, with known rheumatic heart disease and evidence of mitral stenosis and aortic insufficiency. Her heart was enlarged, but prior to this episode of acute rheumatic fever she had never manifested congestive heart failure. This present illness was marked by prominent polyarthritis. In addition, she had a gallop rhythm at the time of admission to the hospital. With salicylate therapy the arthritis subsided, fever remitted and the gallop rhythm disappeared.

In O. G., a thirty-three year old woman, and L. M., a thirty-nine year old woman, both with aortic and mitral valvular disease, congestive heart failure developed in association with acute rheumatic polyarthritis. Following therapy with salicylates and subsidence of the acute rheumatic process, heart failure subsided and has not recurred following the acute illness.

Skin manifestations: Dermatological findings were rare, and erythema marginatum and subcutaneous nodules were entirely absent in this series. An erythema multiforme type of eruption was noted in one patient.

Pharyngitis: An overt pharyngitis at the time of admission was noted in four patients, mild pharyngitis in five, and a normal pharynx in twenty-one.

Fever: Fever was present in all patients at some time prior to treatment. In almost half of the patients the maximum daily temperature prior to treatment exceeded 103°F., and temperatures over 104°F. were not uncommon. In general, the pretreatment temperature curve remained consistently elevated, without showing a diurnal variation.

General malaise and anorexia were often associated symptoms but chilliness or frank shaking chills were uncommon. Only one patient had an epistaxis early in the course of her illness.

LABORATORY MANIFESTATIONS (TABLE VI)

Routine and serial urinalyses were invariably normal. A mild to moderate normochromic anemia was present in approximately half of the patients, particularly in those whose disease was of longer duration. A significant leukocytosis was present in twenty-six patients. The white blood cell count generally ranged between 10,000 and 16,000 per cu. mm. but a count as high as 27,900 per cu. mm. was encountered. The erythrocyte sedimentation rate (ESR) was elevated in all patients. In about three-fourths of the cases the initial ESR was over 80 mm. in one hour, and in five of the thirty the ESR exceeded 120 mm. in one hour. The C-reactive protein was determined in twenty-eight patients. A moderate elevation (2 to 3 plus) was found in ten patients and a marked elevation (4 plus or more) in the remaining eighteen. The antistreptolysin-O titer was normal in 10 per cent of patients (200 units or less), moderately elevated in 58 per cent (250 to 500 units) and markedly elevated in 30 per cent (greater than 500 units).

TABLE VI
LABORATORY FINDINGS IN ACUTE RHEUMATIC FEVER

Findings	Per cent of Patients
Leukocytosis	87
Moderate (10,000–16,000)	70
Marked (over 16,000)	17
Elevated ESR	100
Moderate (21–80)	23
Marked (81–150)	77
Positive C-reactive protein	100
Moderate (2–3 plus)	36
Marked (4 plus or more)	64
Elevated antistreptolysin-O titer	88
Moderate (250–500 units)	58
Marked (over 500 units)	30
Throat culture: beta hemolytic streptococcus	16
Electrocardiographic abnormalities	57
Arrhythmia	13
Prolonged P-R interval	20
T wave and ST segment	37
Chest x-ray abnormality	50
Enlarged heart	46
Pulmonary congestion	3
Pulmonary mottled densities	3
Hypoalbuminemia	15
Hyperglobulinemia	85
Moderate	31
Marked	54

Electrocardiographic Findings. Electrocardiographic abnormalities consisted mainly of arrhythmias, prolongation of the P-R interval, and T wave and ST segment deviations. Twenty-six of the thirty patients entered with regular sinus rhythm. One each showed auricular fibrillation and auricular flutter. One patient demonstrated changing rhythms with sinus arrhythmia, wandering pacemaker, sinoauricular block, and premature auricular and ventricular contractions. One patient had a regular sinus rhythm with frequent premature ventricular

TABLE VII
INTERVAL BETWEEN ONSET OF SYMPTOMS AND START OF TREATMENT

Days	No. of Patients
1–7	9
8–14	8
15–21	5
Over 22	7

TABLE VIII
METHODS OF TREATMENT OF ACUTE RHEUMATIC FEVER IN THIRTY PATIENTS

Drug and Dosage	No. of Patients
Salicylates, 2.4 to 7.2 gm./day	20
Adrenocortical hormones	4
Cortisone, 300 mg./day	1
Prednisone, 30–60 mg./day	3
Salicylates and cortisone	3
Salicylates and prednisone	2
No drug therapy	1

contractions. In the twenty-seven patients with sinus rhythm, the P-R interval was significantly prolonged in only six, usually to between 0.22 and 0.24 seconds. In a single patient the P-R interval was prolonged to 0.40 seconds. T wave and/or ST segment abnormalities were present in the initial electrocardiogram in about one-third of the patients, but in most cases they were due to digitalis or to ventricular "strain" patterns.

Chest Roentgenograms. The chest roentgenogram taken on admission showed normal lung fields and a heart of normal size in sixteen patients. Fourteen patients demonstrated some degree of cardiac enlargement. One patient had a pericardial effusion and one patient (M. A.) had mottled densities distributed in both lung fields, confirmed at necropsy as "rheumatic pneumonia" (Case IV).

Bacteriologic Findings. Cultures of the pharynx revealed beta hemolytic streptococci in only four of the twenty-eight patients in whom such cultures were performed. Blood cultures performed in twenty-three patients were sterile.

Blood Proteins. Serum protein determinations were made in twenty-six patients. A significant hypoalbuminemia (under 3.0 gm. per cent) was found in only four patients. Hyperglobulinemia, on the other hand, was a more common finding, eight patients showing a moderate elevation of serum globulin (3.5 to 4.0 gm. per cent) and fourteen showing a marked elevation of the serum globulin (over 4.1 gm. per cent) with a maximum of 4.9 gm. per cent.

CLINICAL COURSE AND EFFECTS OF TREATMENT

In twenty-nine of the thirty patients drug therapy was started as soon as the diagnosis of acute rheumatic fever had been established; because of the mild nature of her disease, one patient was treated with bedrest alone. In over two-thirds of the patients more than one week had elapsed between the onset of their disease and the time they sought medical attention, and seven patients had noted their symptoms as long as three weeks before seeking treatment. (Table VII.) Once hospitalized, treatment was instituted in most patients on the first or second day of hospitalization.

A wide variety of therapeutic regimens was employed in this series, including salicylates alone, adrenocortical hormones alone, and salicylates and hormones in various combinations. In some cases the initial type of treatment was subsequently modified, i.e., a different drug was substituted for the one used initially or another drug was added. These modifications of treatment were generally the result of an inadequate response to the first drug or the reappearance of signs of rheumatic activity when the first drug was withdrawn. The question of retreatment and the "rebound phenomenon" will be discussed more fully in another publication [6]. Table VIII summarizes the therapeutic regimens employed in this series.

There were two deaths in this series (Cases IV and V). The other patients left the hospital after varying lengths of time completely free of symptoms and signs of rheumatic activity.

The objective findings of joint inflammation disappeared within the first two days of treatment in all patients. Arthralgias, however, persisted in a few patients for three to five days after arthritis was no longer evident but, in general, this symptom too disappeared promptly with the start of treatment.

The effects of therapy on the cardiac manifestations of rheumatic fever were somewhat variable. In the two patients with pericarditis the pericardial rub and effusion disappeared by

TABLE IX
RESPONSE OF CRP AND ESR TO TREATMENT OF RHEUMATIC FEVER

Duration of Treatment for Return of Normal Laboratory Test (days)	Erythrocyte Sedimentation Rate (no. of patients)	C-reactive Protein (no. of patients)
1–7	1	7
8–14	6	10
15–21	6	3
22–28	8	5
Over 29	2	1
Never elevated	0	0
Never returned to normal	7	3
Not available	0	1

the fifteenth day of treatment with prednisone in one patient, while signs of pericarditis in the other patient persisted despite two weeks of cortisone therapy with doses up to 300 mg. daily, subsiding shortly after the addition of salicylates to the regimen. These patients, who were in congestive heart failure on admission, improved with antirheumatic therapy in combination with the usual cardiotonic measures such as digitalis, diuretics and the like. As already noted, a change in the quality or intensity of the cardiac murmurs or the appearance of new murmurs was infrequent. In only two instances did a significant murmur, present on admission, become inaudible after therapy was started. In both cases the change occurred within one week of institution of therapy. In three cases electrocardiographic changes suggestive of pericarditis developed while the patients were on therapy, but there was no clinical evidence of pericardial involvement. Changes in cardiac rhythm were noted in five patients while under treatment; in two, paroxysmal auricular fibrillation with spontaneous reversion to sinus rhythm developed. The one patient who had auricular fibrillation on admission reverted to sinus rhythm spontaneously, and the one patient in whom A-V dissociation was noted reverted to a sinus rhythm prior to onset of treatment. Prolonged P-R intervals in the electrocardiogram generally returned to normal limits by the end of the first week of treatment. When T wave and ST segment abnormalities were not due to digitalis or ventricular "strain" patterns, these deviations returned to normal within two weeks in most cases.

TABLE X
DURATION OF ACUTE RHEUMATIC FEVER IN THIRTY PATIENTS

Duration (mo.)	No. of Patients	Per cent
Less than 1	1	3
1–2	11	37
2–3	10	33
3–4	5	17
Over 4	3	10

Fever subsided promptly with institution of therapy, usually on the first or second day, and in the majority of cases no later than the third day. Tachycardia tended to parallel the fever, slowing of the heart rate occurring concomitantly with the subsidence of fever. In some instances tachycardia persisted despite the presence of a normal temperature and the absence of other clinical and laboratory manifestations of persistent rheumatic activity.

Of the laboratory tests, only the erythrocyte sedimentation rate and the serum C-reactive protein were of value in assessing the response to therapy. A persistent leukocytosis was noted in those patients receiving adrenocortical hormones, even after other symptoms and signs of rheumatic activity had subsided. As shown in Table IX, the disappearance of C-reactive protein from the serum occurred more promptly in response to therapy than did the return of the sedimentation rate to normal.

Side Effects of Therapy. Mild salicylism, as evidenced by tinnitus, nausea and vomiting, was encountered not infrequently but usually responded promptly to reduction of dosage; in no case was complete cessation of salicylates required. The side effects of adrenocortical hormones, on the other hand, were more numerous, particularly in those patients treated with large amounts for prolonged periods of time, Acneiform eruptions and rounding of the face occurred frequently. Glycosuria and elevation of the blood pressure were not encountered.

The duration of the attack of acute rheumatic fever varied greatly. (Table x.) We have defined this duration as the interval between the onset of the first symptoms and the absence of clinical or laboratory evidence of rheumatic activity after antirheumatic drugs were with-

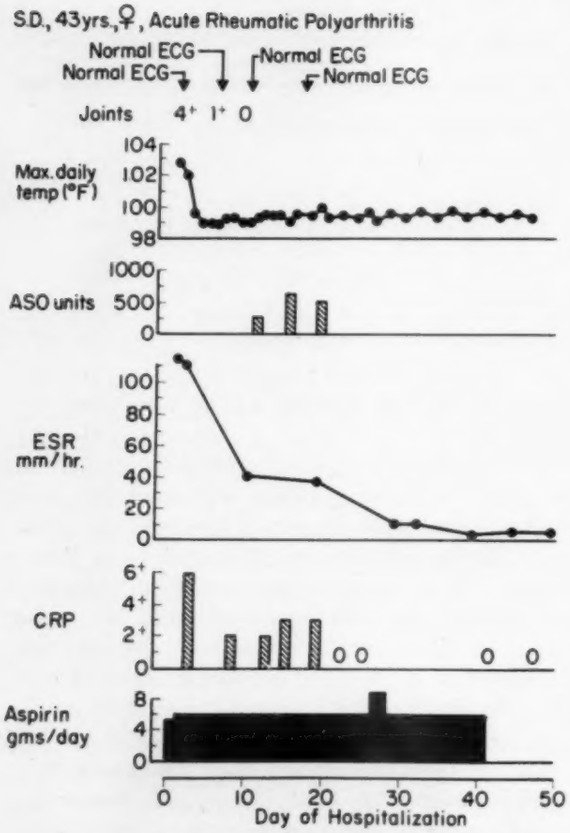


FIG. 1. Case I. Course of illness in patient S. D.

drawn. The significance of this variability in duration of illness in terms of optimal treatment schedules, rebound and relapse will be discussed elsewhere [6].

CASE REPORTS

CASE I. S. D., a forty-three year old white housewife, gave no previous history of rheumatic fever, heart disease or disease referable to the joints. Four weeks before her admission to The Mount Sinai Hospital a sore throat with fever developed, for which she was treated with oral penicillin for five or six days. Two weeks later fever recurred, this time associated with polyarthritis starting at the ankles and progressively involving the knees, wrists, elbows, shoulders and several metacarpophalangeal joints. The joints were hot, swollen, red and tender. Because of the persistence of these symptoms she sought hospitalization.

At the time of admission to the hospital she was acutely ill. The temperature was 102.8°F., the pulse 124 per minute and regular, and the blood pressure 130/70 mm. Hg. The pharynx was not inflamed. The lungs were clear to percussion and auscultation. No masses or viscera were palpated in the abdomen. The heart was not enlarged and the heart sounds were of good quality. No murmurs or thrills were present. Examination of the joints disclosed warmth, redness, swelling and tenderness of both wrists, with tenderness and warmth of the ankles, and effusions in both knees. Skin rashes and subcutaneous nodules were absent.

Laboratory studies demonstrated the urine to be normal. The hemoglobin was 11.2 gm. per cent; the white blood cell count was 13,300 per cu. mm. with an increase of polymorphonuclear leukocytes on differential count. The erythrocyte sedimentation rate (Westergren) was 114 mm. per hour and the C-reactive protein content of the serum was markedly elevated (6 plus). The antistreptolysin-O titer of the blood, 250 units at the time of admission, rose to 625 units during her hospital stay. Culture of the throat disclosed no beta hemolytic streptococci; blood cultural studies were sterile. Lupus erythematosus cell preparations were negative. The latex fixation test for rheumatoid arthritis was negative. Electrocardiogram and chest x-ray film disclosed no significant abnormalities.

The course of this patient's illness is detailed in Figure 1. It was considered that she was suffering from acute rheumatic polyarthritis without demonstrable carditis. Accordingly, salicylate therapy was instituted in doses of 6.0 gm. daily. On this regimen, fever and arthritis promptly remitted. The laboratory indices of inflammation subsided. After six weeks of therapy the drug was withdrawn abruptly. There was neither clinical nor laboratory evidence of a "rebound phenomenon." The patient was discharged from the hospital to be followed in the Outpatient Department and was maintained on penicillin prophylaxis.

Comment: This case is illustrative of those patients in whom a polyarthritis appeared after an upper respiratory infection. In this instance there were neither clinical nor laboratory findings of rheumatic carditis. However, the association of migratory polyarthritis with fever, laboratory evidence of inflammation, serologic demonstration of a recent beta-hemolytic streptococcal infection, absence of laboratory evidence of other arthritides, and prompt response to salicylates with no residua in the joints would appear to justify the diagnosis of acute rheumatic fever.

CASE II. W. J., a twenty-seven year old Puerto Rican woman, was admitted to The Mount Sinai Hospital on September 24, 1957. Two previous admissions, one in 1948 for dental work, the other in 1955 for a normal delivery, disclosed that her heart had been normal both on auscultation and x-ray film. There was no past history of rheumatic fever, arthritis

or cardiac murmur. Three months prior to this hospital admission she had noted migratory joint pains involving the ankles, wrists and metacarpophalangeal joints. Frank arthritis of the knees supervened. Because of persistence of symptoms she was admitted to the hospital.

At this time the patient was acutely ill. The temperature was 101.2°F., the blood pressure was 124/74 mm. Hg and the pulse rate was 100 per minute. The pharynx was normal. The heart was not enlarged, the point of maximal impulse being in the fifth intercostal space within the mid-clavicular line. The rhythm was regular and the heart sounds of good intensity. A faint systolic blowing murmur (grade 1) was present over the pulmonic area. No thrills or rubs were detected. Both knees and the left ankle were warm, swollen and markedly tender; an effusion was noted in the right knee joint.

The urinalysis was normal. The hemoglobin was 13.5 gm. per cent and the white blood cell count 13,100 per cu. mm., with 48 per cent segmented forms and 52 per cent lymphocytes. The erythrocyte sedimentation rate (Westergren) was 64 mm. per hour, the C-reactive protein was 4 plus and the antistreptolysin-O titer was 625 units. L.E. cell test and the latex fixation test were negative. The electrocardiogram taken in the Outpatient Department just prior to admission revealed sinus arrhythmia, wandering pacemaker, sinoauricular block, interference and fusion beats. At the time of admission only a sinus tachycardia was present.

The hospital course of this patient's illness is depicted in Figure 2. It was considered that she had acute rheumatic fever, manifested principally by polyarthritis. Accordingly, salicylate therapy was begun at a dosage of 3.6 gm. daily. There was rapid amelioration of the arthritis and fever. However, the temperature levelled off at approximately 100°F. but with subsequent increase of the dose of aspirin to 7.2 gm. daily the fever remitted completely. The ESR returned to normal by the nineteenth day of treatment and C-reactive protein disappeared from the serum by the fourteenth day of therapy.

At the end of the second week in the hospital it became apparent to all observers that the auscultatory cardiac findings had changed. The faint systolic murmur heard originally along the left sternal border had given way to a harsher, louder and higher pitched, more prolonged, apical systolic murmur, transmitted to the axilla and assuming the characteristics of an "organic" murmur. Serial electrocardiograms during this period revealed occasional premature auricular, nodal and ventricular contractions. Radiographically, there was no evidence of cardiac enlargement. Following withdrawal of therapy there was no recrudescence of rheumatic activity. At follow-up examination one month following discharge from the hospital the patient was asymptomatic. A grade 3, harsh, high-pitched murmur was heard at the cardiac apex

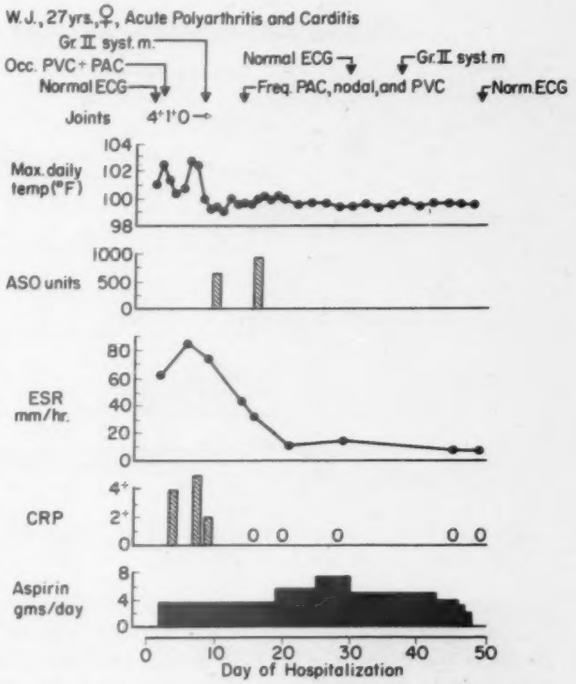


FIG. 2. Case II. Course of illness in patient W. J.

transmitted along the left sternal border and to the axilla.

Comment: This case is similar to Case I in that the patient had acute rheumatic polyarthritis. She had been seen twice previously for unrelated illnesses and had been found free of any cardiac murmurs but subsequently while in the hospital, unlike the patient in Case I, a significant cardiac murmur developed. Thus in this twenty-seven year old woman in the first known attack of acute rheumatic fever an organic cardiac murmur developed and an acute rheumatic carditis may be presumed to have developed.

CASE III. J. S., a twenty-one year old white man, had had chorea at the age of eight, acute rheumatic polyarthritis at age ten, and heart murmurs since that time. He was asymptomatic and had not received chemoprophylaxis prior to the present illness. Ten days prior to admission to The Mount Sinai Hospital he had complained of arthralgias and fever. Two days later a sore throat was noted. He had received unknown quantities of penicillin, oxytetracycline, cortisone and aspirin from his private physician. However, the fever had persisted, arthritis of the knees appeared, and substernal chest pain developed aggravated by deep respiration and relieved by sitting up.

On admission to the hospital he was an acutely ill young man, moderately dyspneic and orthopneic. The temperature was 103°F., the pulse rate was 100

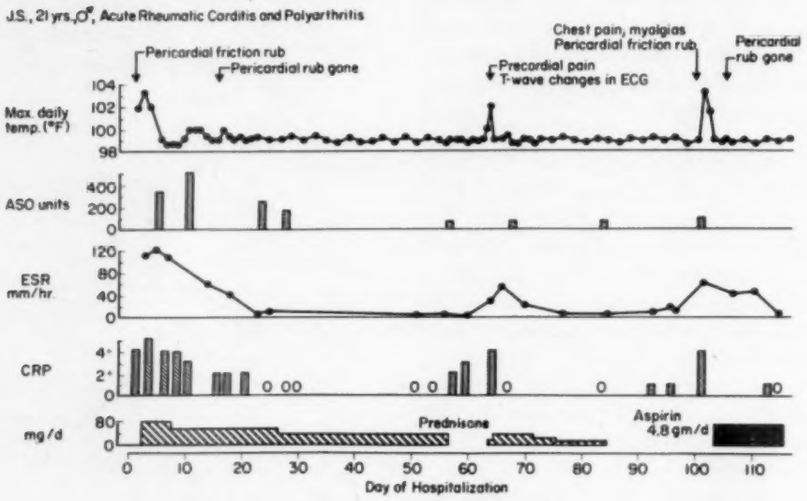


FIG. 3. Case III. Course of illness in patient J. S.

per minute and regular, and the blood pressure was 160/50 mm. Hg. The pharynx was diffusely injected. Dullness and diminished breath sounds were noted at both lung bases and there were scattered inspiratory and expiratory wheezes. The heart was greatly enlarged to the left. A loud to and fro pericardial friction rub was heard at the apex and a gallop rhythm was noted. In addition, a grade 4 systolic murmur and a grade 4 blowing diastolic murmur were heard at the base, a grade 4 blowing systolic murmur transmitted to the axilla, and an early and mid-diastolic rumbling murmur were heard at the apex. The peripheral circulatory findings of free aortic regurgitation were also noted. The only joint finding was slight tenderness of the left ankle.

Laboratory tests disclosed a hemoglobin of 10.8 gm. per cent and a white blood cell count of 12,350 per cu. mm., with 76 per cent segmented forms, 7 per cent band forms and 12 per cent lymphocytes. The urinalysis was normal. The erythrocyte sedimentation rate (Westergren) was 110 mm. in one hour. The C-reactive protein determination was 4 plus. The antistreptolysin-O titer was 333 units on admission, later rising to 500 units. Several blood cultures and lupus cell preparations were negative. The electrocardiogram showed a sinus tachycardia, left axis deviation, a P-R interval of 0.20 seconds and the pattern of left ventricular hypertrophy. The electrocardiographic findings of acute pericarditis were not present.

The hospital course of this patient is charted in Figure 3. It was considered that he had acute rheumatic fever with acute carditis, initiated with typical rheumatic polyarthritis. He suffered from rheumatic valvular disease, with predominant aortic insufficiency and associated aortic stenosis, mitral stenosis and insufficiency.

Treatment was instituted with prednisone administered in doses of 80 mg. per day, and penicillin was given to eradicate any focus of beta hemolytic streptococci. Fever and chest pain disappeared and well-being returned by the third day of treatment although the pericardial rub persisted for fourteen days. The erythrocyte sedimentation rate returned to normal and C-reactive protein was entirely absent from the serum after twenty one days of treatment. The prednisone dosage was reduced at first to 60 mg. and then to 40 mg. daily for four weeks. Following this, therapy was stopped abruptly. He remained asymptomatic for one week but then temperature of 102°F., tachycardia and dull precordial pain reappeared, the erythrocyte sedimentation rate rose to 55 mm. in one hour and large amounts of C-reactive protein were again detected in the serum. Accordingly, prednisone therapy was reinstituted. There was rapid defervescence of the clinical and laboratory abnormalities. The drug was tapered slowly and finally discontinued after four weeks. Eight days later another clinical "rebound" was noted. Salicylates were now given in doses of 4.8 gm. daily. Once again the clinical and laboratory findings abated. He was discharged from the hospital on the one hundred fourteenth day, asymptomatic, to continue on bedrest and salicylates at home.

Comment: This case is a typical example of acute rheumatic carditis in association with less prominent polyarthritis. The illness in this twenty-one year old man was similar to that seen in the childhood form of acute rheumatic fever. It is interesting to note that eleven years intervened between attacks of acute rheumatic fever.

CASE IV. M. A., a thirty year old Negro woman, was admitted to The Mount Sinai Hospital on

September 10, 1957, for evaluation of mitral commissurotomy. She had had an attack of rheumatic fever at age eighteen and had known of a heart murmur since that time. At the ages of twenty-six and twenty-seven years she had had episodes of bronchopneumonia which responded promptly to the administration of antibiotics. For approximately eight years she had noted mild exertional dyspnea increasing in severity in the six months prior to admission. Occasional episodes of paroxysmal nocturnal dyspnea appeared; palpitations and fatigue developed. She had received digitalis and occasional mercurial injections for the preceding two years but was not maintained on a chemoprophylactic regimen. A mild respiratory infection developed characterized by coryza, non-productive cough and hoarseness, and shortly thereafter she was admitted to the hospital.

She appeared to be well developed and well nourished, and in no distress. Her temperature was 99°F., pulse rate 112 per minute, blood pressure 110/80 mm. Hg, and the respirations 14 per minute. The pharynx was not injected. Examination of the lungs revealed numerous scattered inspiratory and expiratory sibilant and sonorous rhonchi. The cardiac rhythm was regular. The first heart sound at the apex and second pulmonic sound were accentuated. There was a grade 3 blowing systolic murmur at the apex transmitted posteriorly and a grade 3 diastolic rumbling murmur well localized to the apex. The remainder of the physical examination was within normal limits.

Laboratory studies showed the urine to be normal. The hemoglobin was 13.6 gm. per cent, the white blood cell count was 8,050 per cu. mm. with a normal differential count. The erythrocyte sedimentation rate (Westergren) was 57 mm. per hour. The antistreptolysin-O titer was 833 units. On radiographic examination the lungs were normal, the heart was enlarged, particularly the right ventricle and left atrium. Electrocardiographic evidence of right ventricular hypertrophy was evident as well as regular sinus rhythm and wide P waves.

The patient was considered to have inactive rheumatic heart disease, enlarged heart, predominant mitral stenosis, possible mitral insufficiency, regular sinus rhythm and congestive heart failure. In addition, an acute and chronic bronchitis was present. Because of the history of an upper respiratory infection preceding admission and the presence of an elevated antistreptolysin-O titer, she was considered to have had a recent beta hemolytic streptococcal infection. Accordingly, she was given large amounts of parenteral penicillin, bronchodilators and expectorants. There was considerable improvement in the cough and pulmonary findings, and she was then scheduled for cardiac catheterization.

On the eighth day of hospitalization (Fig. 4) rapid, regular heart action at 136 beats per minute suddenly developed, unassociated with other changes.

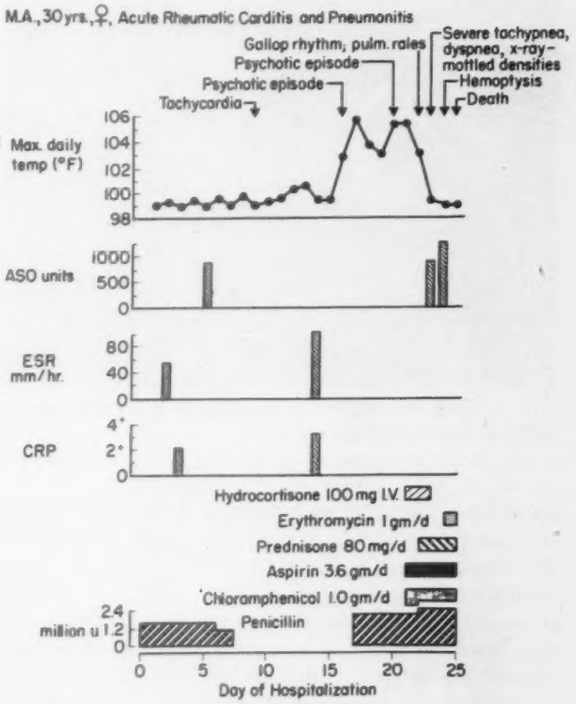


FIG. 4. Case IV. Course of illness in patient M. A.

The electrocardiogram revealed a sinus tachycardia with occasional premature ventricular contractions. Two days later temperature elevation of 100.2°F. to 100.6°F. was first noted. The erythrocyte sedimentation rate had risen to 100 mm. in one hour and the C-reactive protein determination was 3 plus. Sinus tachycardia persisted. On the fifteenth day of her hospital stay there was a striking change in her condition. Active hallucinations appeared, requiring the administration of chlorpromazine for control. The temperature rose to 102.8°F. and subsequently to 105.6°F. A lumbar puncture, cultures of the pharynx and the blood, and studies of sputum, pharynx and blood for influenza virus were negative. The patient was now desperately ill. Severe tachypnea, bilateral pulmonary basal rales and a gallop rhythm were noted. The hemoglobin had fallen to 9.4 gm. per cent and the white blood cell count rose to 20,950 per cu. mm., with 53 per cent segmented forms, 27 per cent band forms, 7 per cent lymphocytes, 5 per cent monocytes, 3 per cent myelocytes and 1 per cent metamyelocytes. The antistreptolysin-O titer was over 1,250 units. X-ray examination of the chest revealed scattered mottled densities throughout both lung fields and a small collection of fluid in the right costophrenic sinus. The heart appeared markedly enlarged but was not suggestive of pericardial effusion. Penicillin, streptomycin, chloramphenicol and erythromycin were administered parenterally. Salicylates failed to modify her course appreciably and physical measures for temperature reduction were relatively

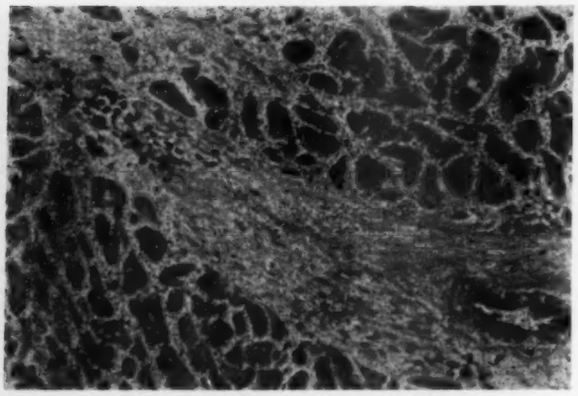


FIG. 5. Case IV. Section of myocardium demonstrating Aschoff bodies and fibrosis.



FIG. 6. Case IV. High power section of Aschoff body from myocardium demonstrating typical fibrillar fragmentation and Anitschkow myocytes.

ineffective. Hemoptysis occurred, of 300 cc. of bloody mucoid sputum containing frank clots. Despite the administration of hydrocortisone intravenously, prednisone orally and anticoagulants, there was a rapid downhill course. Her fever abated but the gallop rhythm and dyspnea persisted. The most striking clinical feature throughout this febrile illness was the tachypnea, with respiratory rates up to 60 per minute. The pulmonary findings fluctuated. At times the lungs were clear to auscultation but later rales returned. She died suddenly nine days after the onset of her terminal febrile illness.

At necropsy it was noted that the heart weighed 340 gm. and was mildly enlarged. A collection of hemorrhagic material uniformly lined and thickened the pericardial surfaces. Numerous petechiae were scattered throughout the epicardium. However, there was no excessive pericardial fluid. The right atrium was slightly dilated. The endocardial surface was smooth and contained no thrombi. The edges of the tricuspid leaflets were slightly thickened and rolled, with small collections of verrucae along the valve margins. The valve commissures were fused but not vascularized. The right ventricular chamber was moderately dilated and its wall and papillary muscles were hypertrophied. The pulmonic valve was normal. The left atrium was mildly dilated, with prominent ridging of the endocardium adjacent to the posterior leaflet of the mitral valve. Marked stenosis of the mitral valve orifice was present, admitting only the finger tip. The valve edges were thickened, rolled, and the commissures fused. Although no verrucae were noted, the leaflets were markedly vascularized. Fusion, thickening and shortening of the chordae tendineae were noted. The left ventricle was normal in size. Thickening and fusion of the aortic valve cusps were present; no verrucae were noted on the valve. The aorta was normal. The myocardium was uniformly firm, and was beefy red in color without areas of discoloration or fibrosis. Histologic sections of the heart revealed large numbers of Aschoff bodies (Figs. 5 and 6) in all areas of the myocardium. Many stages of Aschoff bodies were noted; many were reticular and fibrillar in type, others showed the typical disorganization of the connective tissue with swelling, eosinophilia, granular degeneration or necrosis of the collagenous tissue, surrounded by a cellular reaction consisting of Anitschkow cells, lymphocytes and plasma cells. In other areas, older lesions of fibrotic scarring were noted. The ventricular myocardial fibers were hypertrophied. The endocardium was thickened, most prominently in the left atrium where there were focal areas of fibrinoid degeneration. The tricuspid valve was thickened and vascularized. Both aortic and mitral valve leaflets were thickened. There were numerous pericardial and subpericardial hemorrhages.

The lungs were heavy, firm, generally pale with scattered red mottled areas. On section the parenchyma was greyish white and firm. Many well circumscribed, irregular areas were deep red and softer. The bronchi were congested and contained a thick hemorrhagic mucoid material. On gross examination, the pulmonary arteries and veins were normal. Microscopically, the alveolar septums were markedly thickened by interstitial fibrosis and infiltration with chronic inflammatory cells (Fig. 7), many areas of hyaline membrane formation lining the alveolar walls. (Fig. 8.) Marked proliferation of the alveolar epithelium was noted, with much proteinaceous material and necrotic debris contained within the alveoli, as well as occasional areas of edema and "heart failure cells." There was a moderate degree of peribronchial infiltration by chronic inflammatory cells. Conspicuous muscular hyperplasia was noted in the bronchiolar walls, muscle fibers extending into the alveolar septums. (Fig. 9.) Many of the small arteries showed marked thickening of the intima and media; in certain areas the walls of medium-sized arteries were infiltrated by lymphocytes and polymorphonuclear leukocytes. (Fig. 10.) Gram stain of sections of lung revealed no organisms.

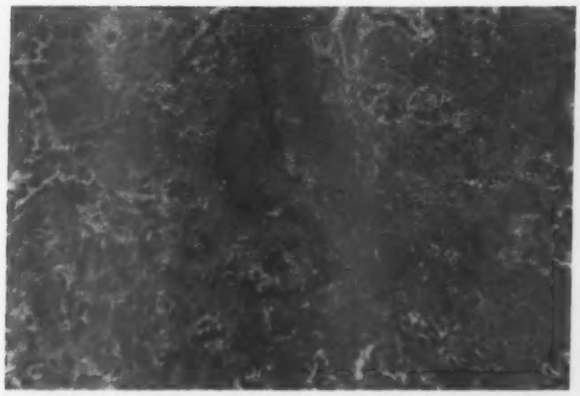


FIG. 7. Case IV. Section of lung demonstrating interstitial fibrosis and infiltration with chronic inflammatory cells.

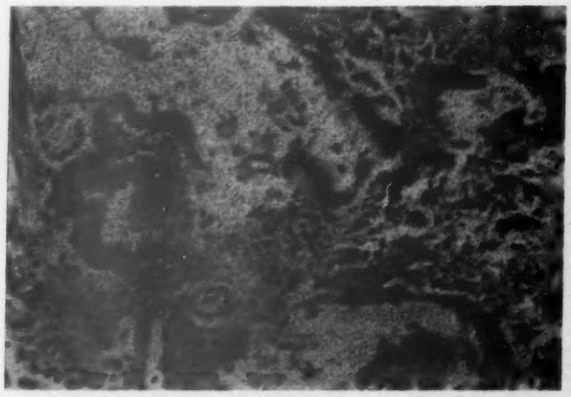


FIG. 8. Case IV. Section of lung showing hyaline membranes lining the alveolar septums.

Acute and chronic passive congestion of the liver and spleen was noted.

Comment: This case in an example of acute rheumatic fever in a patient with rheumatic heart disease, in whom a febrile illness developed and whose clinical condition deteriorated without other obvious cause, such as subacute bacterial endocarditis, multiple pulmonary emboli or intercurrent infection. It is of interest that this patient was observed in the hospital in the latent period between the streptococcal infection and the clinical onset of the acute rheumatic process. The elevated antistreptolysin-O titer might have suggested the proper diagnosis ante mortem.

The pathologic findings of widespread active rheumatic endocarditis and myocarditis substantiate this as an instance of florid rheumatic carditis. The necropsy findings in the lungs, compatible with "rheumatic pneumonia," are sufficient to explain the fulminating pulmonary course.

CASE V. I. S., a forty-eight year old white man, had a history of several episodes of rheumatic fever with polyarthritis in early childhood. Rheumatic heart disease had been evident for many years. At the age of thirty symptoms of congestive heart failure first developed and he had been maintained on digitalis and salt restriction since that time. With self-imposed restriction of activities, he remained relatively asymptomatic on this regimen. One year prior to admission, exertional dyspnea, orthopnea and dependent edema became progressively more severe, and frequent administration of mercurial diuretics was necessary to maintain compensation. Three months before admission he became ill with fever, weakness and slight cough. He was hospitalized elsewhere and was treated with mercurial diuretics, digitalis, blood transfusion and penicillin. After three weeks he felt improved but was still febrile, and was discharged. One month later, dyspnea, orthopnea, abdominal swelling and a non-productive cough reappeared, associated with a small hemoptysis. He was then admitted to The Mount Sinai Hospital.

He was a chronically ill-appearing, pale, apprehensive, dyspneic adult male. The temperature was 102.8°F. and the blood pressure 152/75 mm. Hg.

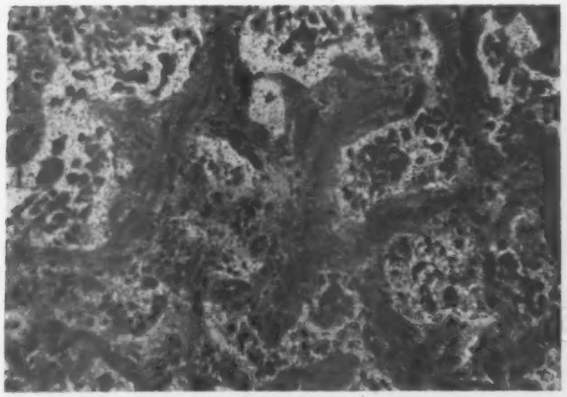


FIG. 9. Case IV. Section of lung demonstrating muscular hyperplasia of alveolar septums.

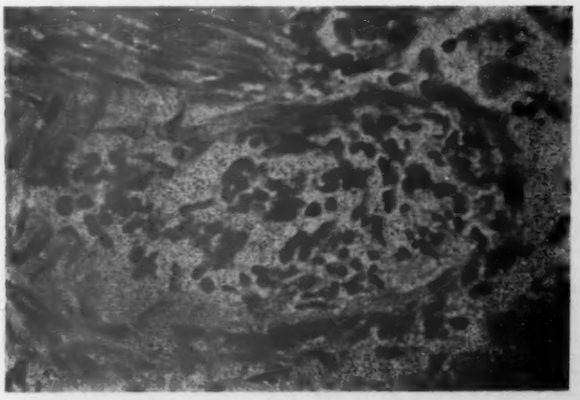


FIG. 10. Case IV. Section of medium-sized artery in lung demonstrating acute arteritis.

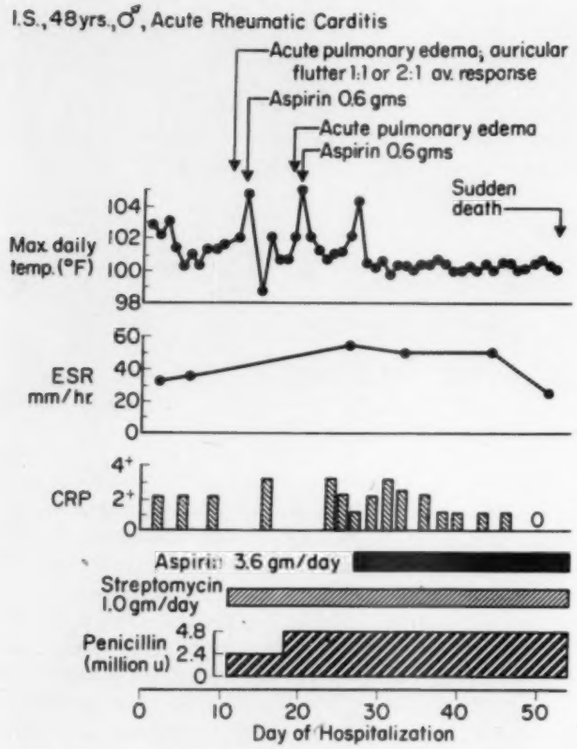


FIG. 11. Case v. Course of illness in patient I. S.

The neck veins were distended, with a prominent hepatojugular reflex. The lungs were clear to percussion and auscultation. The heart was greatly enlarged, the point of maximal impulse was in the fifth intercostal space at the anterior axillary line. The cardiac rhythm was regular at a rate of 80 per minute. Prominent systolic and diastolic murmurs at the mitral and aortic areas, characteristic of mitral stenosis and insufficiency and aortic stenosis and insufficiency, were noted. The liver was firm, nontender, and extended 4 cm. below the right costal margin; a firm spleen was palpated 2 cm. below the left costal margin. Peripheral edema, clubbing of the fingers and petechiae were absent.

Laboratory examination disclosed a hemoglobin of 11.4 gm. per cent, white blood cell count of 8,000 per cu. mm. with a normal differential count. The urine contained 2 plus albumin but was otherwise normal. The erythrocyte sedimentation rate (Westergren) was 32 mm. per hour and the C-reactive protein was 3 plus. The antistreptolysin-O titer was 333 units. Serial blood cultural studies were sterile. The electrocardiogram revealed auricular flutter with a 4:1 A-V response, ST segment and T wave abnormalities compatible with digitalis effect and myocardial damage. Generalized cardiac enlargement was noted radiographically. Venous pressure and circulation time studies with Decholin® were markedly abnormal, indicative of severe heart failure.

The hospital course is portrayed in Figure 11. It was considered that this patient was suffering from rheumatic heart disease, mitral stenosis and insufficiency, aortic stenosis and insufficiency, congestive heart failure and atrial flutter. Accordingly, therapy was directed toward control of the heart failure by the use of digitalis, diuretic agents and salt restriction. Most observers initially were of the opinion that his fever and the deterioration of his clinical state were attributable most likely to subacute bacterial endocarditis. The fever persisted and, despite negative blood cultures, antibiotic therapy was instituted on the tenth hospital day. Large doses of penicillin and streptomycin were given parenterally. During the next two weeks the course of the fever was essentially unchanged. Two episodes of pulmonary edema occurred, associated with atrial flutter with a 1:1 and at times 2:1 ventricular response. Additional drug therapy resulted in return to a more stable atrial flutter-fibrillation rhythm with a slower ventricular rate.

After seventeen days of antibiotic therapy it became apparent that there was no change in the patient's clinical condition. The diagnosis of active rheumatic fever was then considered. Accordingly, salicylate therapy consisting of 3.6 gm. daily was added to the regimen. There was a prompt fall in the temperature curve to a maximum of 100.4°F. to 100.6°F. daily. His clinical state also appeared to improve. His heart failure was more easily controlled. The cardiac rhythm stabilized at atrial flutter with a 4:1 response. There was improvement in the levels of the erythrocyte sedimentation rate, which had been 55 mm. per hour prior at the start of salicylate therapy, falling to 22 mm. per hour three weeks later. C-reactive protein diminished and finally disappeared from the blood.

On the fifty-first hospital day, while apparently doing well clinically, he suddenly died.

Necropsy findings were as follows: The heart was markedly enlarged and weighed 680 gm. The pericardial cavity contained 75 cc. of clear, straw-colored fluid. The pericardial surface was smooth except at the apex where it was opacified and thickened. The right atrium was dilated and hypertrophied. The tricuspid valve was dilated. Its leaflets were thin, pliable and discrete, with minimal thickening of the auricular surface of the middle cusp. The right ventricular cavity was dilated and its wall moderately hypertrophied. The endocardium of the right chambers was normal and contained no thrombi. The pulmonic valve was normal. The left atrium was hypertrophied but not dilated. An adherent, flat, lamellated thrombus was present in the left atrial appendage but was covered by smooth endocardium. The remainder of the left atrial endocardium was thick and opaque, with raised plaques on its posterior surface. The mitral valve orifice was stenotic, admitting a finger tip. The cusps were fused, thickened and

shortened; calcification of the ring and valve was noted. The overlying endocardium was smooth. The chordae tendineae were fused and shortened, and inserted into the ventricular surface as well as into the free margins of the valve. The left ventricle was hypertrophied and dilated. At the apex an aneurysmal dilatation of the left ventricular wall was present, measuring 3 mm. in thickness as compared to a left ventricular thickness of 2.0 to 2.5 cm. elsewhere. At this site the endocardium was thickened and dense, and the myocardium fibrotic. Other sites of endocardial fibrosis were noted in the outflow tract. The aortic valve cusps were fused, thickened, deformed and calcified. The coronary arteries were narrowed, due to atherosclerosis, but no occlusion of the lumen was demonstrated. Histologic sections of the heart revealed evidence of old valvulitis of the mitral and aortic valves, with no evidence of cellularity. Throughout the myocardium, particularly in the subendocardium, there were numerous Aschoff bodies with connective tissue fragmentation, fibrosis and typical cellular reaction. In addition, focal myocardial and perivascular fibrosis was demonstrated. The left atrium revealed fibrotic musculature with subendocardial cellular infiltration. A large organizing thrombus of the left atrial appendage was noted. Moderate endocardial sclerosis was present throughout. The coronary arteries were the site of moderate occlusive atherosclerosis.

Additional necropsy findings included atherosclerosis of the pulmonary artery, acute and chronic congestion of the lungs, liver and spleen, and old multiple infarctions of the lungs, spleen and kidneys. The terminal episode appeared to be acute edema of the lungs.

Comment: In this instance, subacute bacterial endocarditis was thought to be responsible for this patient's illness (a common error) and only after the failure of antibiotic therapy to modify the course was acute rheumatic fever considered. Salicylates partially ameliorated the clinical and laboratory manifestations. Unfortunately, as clinical improvement appeared well established, death suddenly intervened.

COMMENTS

Incidence. The mean age of the initial attack of acute rheumatic fever has been variously reported, depending largely upon the age group under study. If all age groups are considered, the peak incidence is between eleven and seventeen years [*7–11*]. The present study was limited to patients over the age of twenty-one. It is of interest that 50 per cent of our patients were in the third decade; the oldest was fifty-nine. Of the fourteen patients with the first known attack of rheumatic fever, without antecedent heart disease, seven were in the third decade and the remainder in the fourth and fifth decades. The oldest person to have a first known attack was a forty-six year old white man.

One of the principal features of rheumatic fever, its tendency to recur, was evident in the present series in which over half of the cases represented recurrent episodes. The risk of recurrence apparently diminishes progressively with the age of the patient as well as with the period of time which has elapsed since the previous attack. Wilson and Lubschez [*13*], in a series of 499 rheumatic patients, found 817 recurrences; 20.6 per cent occurred in the first year following an attack, 10.7 per cent one to two years after an attack, and only 6.6 per cent two or more years following an attack. On the other hand, Mortimer and Rammelkamp [*12*], in a study of seventy-seven rheumatic subjects with streptococcal infections, found that the recurrence rate of rheumatic fever following such infection did *not* significantly decrease with elapsed periods since the previous attack. In studies by Bland and Jones [*9*] and Cohn and Lingg [*14*] significant recurrence rates were noted as late as fifteen to twenty years after the original attack. It is evident that even the adult who has enjoyed freedom from acute rheumatic fever for many years runs the risk of recurrence. Indeed, in one patient in the present series there was an interval of thirty-five years between attacks.

The present experience is consistent with the established view that antecedent streptococcal infection is as important in the development of acute rheumatic fever in the adult as in childhood. Stollerman et al. [*15*] determined antistreptolysin-O (ASO), antihyaluronidase (AH) and antistreptokinase (ASK) titers in eighty-eight patients with rheumatic fever and found that 95 per cent had elevation of one of these antibodies to the streptococcus. Unfortunately, the streptococcal infection is not always clinically evident and even when present is often inadequately treated. No patient in this series received adequate chemotherapy preceding the onset of acute rheumatic fever. Studies by many groups [*16–18*] have since shown conclusively that prompt and vigorous treatment of a streptococcal infection with antibiotics significantly decreases the incidence of subsequent rheumatic fever.

Manifestations. Fever is undoubtedly the

most common manifestation of this disease in the untreated patient, with temperatures over 102°F. the usual finding, and hyperpyrexia (over 104°F.) not uncommon. An almost immediate fall in temperature with institution of appropriate treatment is the general rule.

In the present series, symptoms and findings referable to the joints were the second most common manifestation. In 93 per cent of the cases the disease was heralded by arthralgias or arthritis as the initial manifestation. Arthralgias were present in 93 per cent at some time prior to treatment and objective evidence of arthritis was noted in 87 per cent. As in the classic descriptions of acute rheumatic fever, the arthritis most often was migratory, with multiple joint involvement, the large joints of the lower extremities being most often affected, sometimes with frank effusion. However, biarticular rheumatism did occur and in many instances the atypical nature and distribution of the joint manifestations compelled one to carry out tests appropriate for the exclusion of rheumatoid arthritis, systemic lupus erythematosus, sickle cell anemia and other arthritides.

The incidence of acute carditis in this series is more difficult to determine because many patients with previous rheumatic heart disease are included. The mere presence of murmurs obviously does not establish a diagnosis of active rheumatic carditis in these cases. Likewise, a fixed arrhythmia or the presence of cardiac enlargement does not help in the diagnosis. Prolongation of the P-R interval may be the residuum of a previous episode of carditis or due to the administration of cardiac drugs, and alterations in the T waves and ST segments are often ascribable to digitalis, quinidine, and ventricular hypertrophy and "strain" patterns, and thus rarely are useful as an index of activity. In agreement with others [*19*], we have not found measurement of the Q-T_c interval valuable either as an aid to diagnosis or in management of the disease.

The Jones criteria [*5*] for the diagnosis of acute rheumatic carditis are as follows: (A) The presence of a significant apical systolic murmur, apical mid-diastolic murmur or basal diastolic murmur in a patient without a history of previous rheumatic fever or in whom there is good reason to believe there was no pre-existing rheumatic heart disease, or a change in the character of any of these murmurs under observation in a patient with previous history of rheumatic fever or rheumatic heart disease. (B) Obviously increasing cardiac enlargement as evidenced by x-ray examination. (C) Pericarditis manifested by a friction rub, pericardial effusion or definite electrocardiographic evidence. (D) Congestive heart failure (in a child or young adult under twenty-five) in the absence of other causes. Employing these standards, it was concluded that active rheumatic carditis was present in ten of the thirty patients, or 33.3 per cent. Two additional patients (I. S. and M. A.) did not necessarily fulfill these rigid clinical criteria but at necropsy were found to have widespread, unequivocally active rheumatic endocarditis and myocarditis. Two additional patients (L. M. and O. G.) are included in this group of patients because of the appearance of congestive heart failure for the first time in association with acute rheumatic polyarthritis. With these additional four patients the incidence of carditis is increased to 46.7 per cent. Acute carditis was somewhat more common in the patients with recurrent rheumatic fever. Nine of the sixteen patients with pre-existing heart disease manifested carditis, whereas only five of the fourteen patients with first known attacks had carditis. There was no significant age difference between the groups with and without carditis; it was observed in one male in his initial attack at age thirty-nine, and in another at age forty-six.

The considerably greater incidence of arthritis as compared to carditis in adult rheumatic fever deserves emphasis since quite often rheumatic fever is mistakenly excluded from the differential diagnosis of a polyarthritis when evidence of cardiac involvement is lacking. It should be borne in mind that the relative incidence of these two major manifestations is distinctly related to the age group under study. Bland and Jones [*9*] found carditis to be more prevalent than arthritis in persons with rheumatic fever who were under the age of twenty-one, and similar findings were noted in the United Kingdom-United States study which was concerned with patients under the age of sixteen [*10*]. On the other hand, when a series includes young adults (Lieber and Holoubek [*11*], Bruce [*8*], Joos and Katsampes [*7*]), or excludes children entirely, as in our series, arthritis appears to be the more common manifestation.

Similarly, chorea, completely absent from our series, is a manifestation more commonly

encountered in childhood. Erythema marginatum, considered by some as highly suggestive of acute rheumatic fever and even diagnostic of the disease, was present in none of the patients in this series. Other reported series also cite a very low incidence (0.6 to 9.5 per cent) of erythema marginatum when the older age groups are included. Subcutaneous nodules, absent in our cases, occurred in 3 to 10 per cent of patients in previously reported series.

Table XI demonstrates the incidence of three of the major manifestations of acute rheumatic fever in selected series.

TABLE XI
INCIDENCE OF THREE MAJOR MANIFESTATIONS OF RHEUMATIC FEVER IN VARIOUS AGE GROUPS

	Pader, Elster	Lieber, Holoubek [11]	Joos, Katsampes [7]	Bland, Jones [9]	United Kingdom–United States [10]
Age group (yr.)	21–59	3–39	4–24	under 21	under 16
Carditis (%)	46.7	56.2	44.5	63.5	76.4
Arthritis (%)	86.6	63.6	72.2	41.0	43.3
Chorea	0	9.3	19.4	51.8	10.9

In reviewing the manifestations of acute rheumatic fever in our thirty patients it is apparent that certain criteria of diagnosis must be modified as the disease applies to the adult patient. The presence of arthritis and/or carditis is, of course, necessary for the diagnosis. The differentiation of the arthritis of acute rheumatic fever from other arthritides still poses a problem, but its migratory nature, the polyarticular involvement, its relationship to a recent streptococcal infection and the lack of chronic joint change favor the diagnosis of acute rheumatic fever. The problems of diagnosis of carditis in the adult patient have already been enumerated. The association of carditis with polyarthritis is highly suggestive of acute rheumatic fever. The absence of chorea, subcutaneous nodules and erythema marginatum from this series of cases reduces the value of these findings as aids in diagnosis. The minor criteria for the diagnosis of acute rheumatic fever are not pathognomonic and often cannot distinguish this disease from other acute inflammatory diseases involving the joints. Acute phase reactants, arthralgias, even prolongation of the P-R interval on the electrocardiogram, may be non-specific.

Laboratory Findings. Of the laboratory aids employed in the diagnosis and management of rheumatic fever, the leukocyte count is the least useful. A leukocytosis almost invariably occurs in patients receiving adrenocortical hormones, and usually persists so long as the hormones are continued, in spite of obvious clinical improvement. The erythrocyte sedimentation rate (ESR) is of established usefulness but has certain deficiencies; its range of normal is poorly defined; it is affected by anemia, plasma protein alterations and by congestive heart failure. It is relatively insensitive to changes in clinical condition. We share the opinion of most workers in the field [*20,21*] that the determination of C-reactive protein (CRP) in the serum by the capillary precipitin method is the most valuable guide to the treatment and management of acute rheumatic fever. It was found to be generally more sensitive than the ESR, to disappear from the serum more quickly in the early recovery period, and usually to reflect changes in the patient's condition more promptly. The value of the C-reactive protein test is limited by its non-specificity and its appearance in the blood of patients with uncomplicated congestive heart failure [*22*]. The antistreptolysin-O titer has great usefulness in the differentiation of rheumatic fever from other arthritides by demonstrating the presence of an antecedent streptococcal infection.

Hypoalbuminemia and hyperglobulinemia may occur in acute rheumatic fever. In sixty cases of acute rheumatic fever Jacox [*23*] attempted a quantitative assessment of the inflammation by periodic determination of the plasma proteins and their correlation with the CRP and ESR. During the acute phase he observed an increase in the alpha-globulin and fibrinogen and a decrease in albumin. The ESR and CRP often became normal while the alpha-globulin remained elevated. He concluded that the alpha-globulin is a more sensitive index of inflammation than the other two tests. In other studies [*24*] a considerable increase in the gamma globulin early in the disease, and a fall to normal levels with subsidence of activity have been reported.

Clinical Course. In general, the more acutely ill patients with clinical evidence of carditis received the adrenocortical hormones. The remainder received salicylates except for the one patient who was given no drug therapy.

It is our impression, in conformity with that of others [*10*], that the adrenocortical hormones

were not distinctly superior to salicylates in suppressing the acute manifestations of the disease. However, since the possible preventive effect of hormones on the ultimate cardiac damage is still an unsettled question, we employed them alone or in combination with salicylates when there was unequivocal evidence of carditis. Aside from mild salicylism in a few patients, which responded promptly to reduction in dose, and the appearance of a "cushingoid facies" in patients receiving hormones, there were no significant side effects of treatment.

We endeavored to institute treatment as soon as the diagnosis was established. However, many patients did not seek medical care immediately after onset of their symptoms and in some cases first received inadequate suppressive therapy (usually aspirin) with partial relief of symptoms, thus delaying adequate treatment for several days or weeks. The importance of early treatment is emphasized by the findings of Massell and others [*25,26*], that the effect of hormone therapy in preventing valvular damage, at least as judged by the disappearance of murmurs under therapy, is quite definitely related to the duration of illness prior to the onset of therapy, and that decrease in cardiac enlargement appears to depend to a large extent on the duration of the disease at the time that hormone therapy is begun.

No statement is possible at this time concerning the incidence of valvular damage following the attack of acute rheumatic fever in our adult patients. The incidence of acute carditis in the adult appears to be less than in childhood and it is possible that the incidence of valvular disease also may be less in the adult group. No acceptable data on this point are yet available.

SUMMARY AND CONCLUSIONS

1. The clinical and laboratory manifestations of acute rheumatic fever in thirty patients over the age of twenty-one years are described.

2. Acute rheumatic fever not infrequently occurs in the older age groups, either as an apparent first attack or recurrently, in the latter instance often after an interval of many years.

3. The difficulties inherent in establishing a diagnosis of acute rheumatic carditis in the adult patient, notably in those with pre-existing rheumatic valvular disease, are discussed.

4. Rheumatic fever in the adult differs from childhood rheumatic fever in the higher incidence of arthritis as compared to carditis, and the extremely low incidence of subcutaneous nodules, chorea and erythema marginatum.

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Review

Kuru*

Clinical, Pathological and Epidemiological Study of an Acute Progressive Degenerative Disease of the Central Nervous System among Natives of the Eastern Highlands of New Guinea

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In early March 1957 we initiated in a mountain-dissected region of the Eastern Highlands of the Australian Trust Territory of New Guinea an intensive study of a neurological disease syndrome new to Western medicine. This disease is clinically akin to the chronic progressive heredofamilial degenerative disorders of the central nervous system, particularly the cerebellar and spinal ataxias and the degenerations involving the corpus striatum, and to certain chronic poisonings, especially that with manganese. The disorder affects exclusively the Fore people and their immediate tribal neighbors. Among these Melanesian Highland natives it has attained an extraordinarily high incidence, accounting in recent years for almost half the deaths that occur in their communities. We have presented elsewhere details of our initial discovery and description of this disease [*1–3*]. In this report we shall review the clinical and pathological findings obtained from an intensive investigation of our first 200 cases of this disease and our epidemiological observations of these cases and of an additional 600 cases of Kuru which we have been able to document.

Kuru, as the disease is known by the Fore, is a word also used by them to designate the trembling associated with fear or cold. Among the Kimi people the disease is called Uruna.

GEOGRAPHICAL DISTRIBUTION

Kuru has been observed only in a mountainous region in the Eastern Highlands of the Australian Trust Territory of New Guinea south and east of Mt. Michael (elevation 12,500 feet) and some 30 miles southwest of Kainantu where the homeland of the Fore linguistic and cultural group is located. These people and the tribes which surround them have been pacified only during the past five years, and intertribal and intervillage warfare, ritual killings, sorcery and cannibalism, which included the eating of many of those who died, have all been discouraged by the government. However, remnants of warfare and cannibalism still survive, and sorcery and ritual killings, often in reprisal for Kuru magic, remain the dominant administrative problem in the area. The Kukukuku type people who border the Fore people on the southeast along the Lamari River remain uncontrolled and their rugged country is still incompletely explored. To the south the Fore are bordered by uninhabited forested ranges dropping from the Highland drainages of the Yani and Lamari Rivers to the lowland sago jungles, homeland of the Bird of Paradise. Here, in the foothills to the New Guinea Highlands, the Yani and Lamari unite into the Subu (or lower Lamari) River. The Subu shores are inhabited by the Yar subgroup of the Pawaian linguistic group, who inhabit the upper Purari River shores of Papua.

This region is administered from the Okapa Patrol Post which was established in 1954 and is in communication with Kainantu by wireless and by a rough 40 miles of "jeep" road. This patrol post is situated in approximately the geographic and population center of the Fore people, some 11,000 in number, and from it a total of some 30,000 natives are censused. All cases of Kuru have occurred in or adjacent to

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this division of the Kainantu Subdistrict of the Eastern Highlands; and nowhere in Papua or New Guinea where continuous medical observation of native populaces has been in progress for over twenty years (i.e., in such places as Port Moresby, Lae, Madang, Bulolo, Wau, Goroka and Mt. Hagen) has a verified case of this disease occurred.

Within the region the disease is clearly one of the Fore people. Every Fore village and hamlet has a history of recent Kuru deaths; and very few are lacking a currently active case of Kuru included in our Kuru study series. The disease thus occurs in the entire region inhabited by the Fore cultural and linguistic group and in addition extends into the neighboring linguistic and cultural groups of the Auiana, Usurufa, Kanite, Keiagana, Iate, Kamano and Kimi peoples. Furthermore, a small group of 700 Iagaria people, whose tribal lands are on the western slopes of Mt. Michael but who migrated to this region east of Mt. Michael several generations ago and have extensively intermarried with the Fore into whose territory they moved, are also affected with Kuru. In the areas administered from neighboring government centers of Lufa (west of Mt. Michael), Kainantu, Menyamya (to the southeast), and Kerema (on the Papuan coast) no Kuru has developed. In the adjacent region administered from Henganofi, to the northwest, the disease has occurred only in those villages bordering on the Kuru region in the Okapa administrative district. In each of the Fore-neighboring groups Kuru affects only the portion of the population immediately adjacent to the Fore. More remote settlements of these other peoples, who do not intermarry with the Fore, have not experienced Kuru. Iate, Kanite and Usurufa groups are small populations, all portions of the land they occupy lying close to Fore Kuru-affected populations, and all the villages of these small groups have a history of Kuru. All the Fore neighbors, except the Kukukuku across the Lamari River and the Yar people of Pawaian stock from Papua, are thus far known to have Kuru in those settlements bordering on the Fore. The Kukukuku are separated from the Fore by the formidable barrier of the Lamari River and have no marriage contacts with Fore villages other than two recent marriages of Fore women into Kukukuku hamlets. Ecologically, however, the Lamari forms no discontinuity, and variations of terrain, elevation, vegetation and rainfall are greater within the Fore lands than at any of the boundaries between Kuru and non-Kuru areas. The Yar people to the south are separated from the Fore by three days' of hard walking through dense forests and likewise have little marriage contact with the Fore—that which they have being limited to one recent marriage with a Fore woman. However, they visit the Fore people frequently and have recently adopted into the Yar village four Fore youngsters. It is of interest that during intertribal fighting, the Fore people of Kasarai—the most southerly of the Fore villages—moved southward temporarily toward the Yar people to settle for over a decade at Abonai, which is in sago palm country, probably under 2,000 feet elevation. While living here in sago jungles they still had Kuru deaths among their women.

The Kuru area ranges from 3,000 to 7,000 feet in elevation and its mountainous terrain is dissected by broad, deep valleys. Most ranges are heavily forested on their summits and these forests extend down into the valleys in some places. Kunai grass-covered slopes predominate, however, at the lower elevations. The Fore people live both in settlements on these kunai slopes and in small hamlets in the forests. Kuru follows them from the lowest and most open of their settlements to the highest forest-hidden hamlets.

The accompanying map (Fig. 1) illustrates the location of the Kuru region in New Guinea with respect to all places thus far mentioned in the text. A more detailed map of the Kuru-affected region, showing the extent of Kuru within each linguistic and cultural group, will be presented in the discussion of Kuru epidemiology.

HISTORIC BACKGROUND

The first recorded entry of Europeans into the Fore region is the expedition in 1936 of Ted Ubank, a gold prospector. On this occasion large pine forests were discovered at Okapa which are now used as a source of seed for Highland forestation. In 1949 a Lutheran Mission was set up at Tarabo in the Keiagana linguistic area and when the government established its first patrol post, called Kumiawa, in the region in 1952 it selected the same site. In 1954 the administrative center was moved to the Moke-Pintogori region in the center of the Fore linguistic and cultural group and incorrectly named the Okapa Patrol Post. Until the initiation of our Kuru research project the Okapa Patrol Post



FIG. 1. The Kuru region in the Eastern Highlands of Australian New Guinea.

was a seldom-visited outpost from which 30,000 natives were censused and administered, and in the entire region only two Europeans were resident: the missionary at Tarabo and the government patrol officer.

Patrol officers noted Kuru, referred to as *skinguria* in Pidgen English, in their patrol reports as early as 1953; and it soon became apparent to succeeding government officers in the region that "the shaking disease" was the major medical problem in the area. In 1951 and 1953 R. M. and Mrs. Berndt, doing anthropological and linguistic field work in the linguistic blocs of Kamano, Usurufa, Jate and Fore, noted the illness among the Fore, Jate and Usurufa peoples [*3b*]. The disease was brought to the attention of one of us (V. Zigas) in 1955 and an effort was made to study it and determine its cause. Early in March 1957 we joined forces and inaugurated an intensive study of Kuru at Okapa. A special native materials hospital was quickly erected to house the Kuru patients whom we assembled, and a laboratory and treatment room was built in which examinations and studies could be conducted. Jeep transport provided a means of sending specimens out to the airstrip at Kainantu from where they were flown for special studies to laboratories in Port Moresby, Australia and the United States. The Kuru Research Center which was thus set up subsequently proved to be located very close to the geographic and population center of the Kuru region. Eighty-five Kuru patients have been intensively studied here by clinical and laboratory investigations, and therapeutic trials with numerous drugs have been conducted. In addition, case finding and epidemiological patrols were launched from this center to all parts of the Kuru region and into the surrounding territory. On such patrols another sixty-five patients have been thoroughly studied in their village setting. The remaining fifty patients in our series of studied cases have not been fully examined and, in some instances are documented as cases which have developed and in which death has occurred during our period of Kuru study, having been seen only by our native medical assistants. We have, in addition, operated a native hospital (servicing the entire region administered from Okapa) to which there have been over 1,000 admissions during the first ten months of Kuru research. Here, with the help of the Commonwealth Film Unit, a motion picture film has been made showing the clinical features of each of the stages of Kuru. In addition, a ciné record of the progression of the illness from early ataxia to incapacitation and death in many of the patients has been kept, and films have been made documenting the prominent place of the disease in Fore culture.



FIG. 2. Kimi wives in mourning. They were all married to a prominent village leader whose death they mourn by covering themselves with mud and "rags" of old capes made from knotted bark fibers.

ETHNOGRAPHIC SETTING

The Fore and surrounding people are Melanesian natives experiencing their first European contacts. Although most have seen Caucasians during the past five years, few had seen European women or children until our center was visited by European families. Figure 2 illustrates the mourning of women of the Kimi tribe, neighbors of the Fore people who also suffer from Kuru. To these natives, Kuru, like most disease, is the result of magic, and Kuru sorcery occupies a very significant place in the total fund of Fore sorcery. Kuru is worked upon its victims usually in response to some real or imagined wrong, such as failure to respond to courting overtures, and for this purpose the sorcerer—who may be any male member of the community—requires a portion of the victim's person, excreta, clothing or discarded food. Feces are most often used, but hair, skin from sweet potato eaten by the victim, a piece of the victim's "maro" (or bark shirt) are often employed. This material is carefully packaged in leaves and bark, tied with vine, and placed partially submerged in a swamp. The sorcerer then visits this half-buried charm and shakes it each day until his victim commences to shake with the "shaking disease," Kuru. Thereafter the charm is left to decay in the swamp. Once started, Kuru usually follows a relentlessly progressive course to death, and in most Fore communities one is told that it is never cured. However, in certain communities in which cures or recoveries are known, these are readily explained: (1) The sorcerer has relented, and has removed his charm. (2) The sorcerer has been discovered or revealed himself and has been bribed to hand over his charm to the kinsmen of the afflicted. (3) The sorcerer has been discovered, often by magical divination, and forced or bribed to execute counter-magic. (4) The process of devination has been used to locate the site of implantation of the Kuru charm and the charm has been thus discovered and destroyed. This divination in order to discover the site of burial of the Kuru charm usually takes the form of collecting waters from



FIG. 3. A Fore victim of Tukabu who has been attacked by a group of the relatives of a Kuru patient whose disease they attributed to his sorcery. His trachea has been bitten and his femurs, renal areas and genitalia have been pounded with stones. This vendetta directed against male sorcerers serves, to some extent, to balance the predominantly female mortality from Kuru.

numerous springs and offering these to the patient. When the water from near the offending site is consumed, violent vomiting and retching ensues, and the location is thus established. The site may then be closely watched to note who approaches it for the purpose of visiting and shaking a charm. On the other hand, the village or hamlet to which the sorcerer belongs may be determined by roasting numerous small rats, each in a bamboo cylinder, in a cooking fire. Each beast is arbitrarily assigned representation of a community under suspicion. After cooking, the animals are opened, and that animal with particular discoloration and changes in its viscera is taken as indicating the offending clan. Occasionally bribery may then be resorted to in order to purchase the Kuru-invoking charm. More usually, reprisal in the form of warfare (in the past) and ritual vendetta murder (in the past and present) are resorted to. Such reprisal usually takes the form of "tukabu," a culturally dictated form of ambush, on the first members of the offending clan to appear or on a particular individual suspected of having worked the Kuru magic, in which the means of assault are formalized and fully prescribed by tradition: pounding of the humeri and femurs and of the renal areas with stones, pounding of the anterior neck with stones or wooden clubs, biting of the trachea until it is fractured, and crushing of the external genitalia with stones and clubs.

We have seen victims of tukabu after they had been so dealt with and died, and others who have been brought to us in severe distress from a recent tukabu attack which had been interrupted by the appearance of the victim's clansmen. (Fig. 3.)

Thus, Kuru accounts for more deaths than those of its immediate victims, for in the past, as at present, a considerable number of people are murdered in reprisal for having worked or been suspected of working Kuru magic. In addition, Kuru victims are often women with nursing infants, and upon the death of the mother such children usually die of malnutrition, for the Fore people have not generally accepted the practice of transferring the infant to another nursing woman. Kuru magic is traditionally the property of the Fore people and those surrounding peoples who suffer from Kuru attribute to the Fore, or to their own men instructed by the Fore, the sorcery responsible for Kuru in members of their communities.

CLINICAL PICTURE

Kuru is remarkable for the uniformity of its symptomatology and clinical course. In fact, so unvaried is the clinical pattern that its stages are



FIG. 4. A group of six Kuru victims, all still ambulatory. These five women and one girl, clothed in typical Fore feminine dress, were from the village of Pa'iti. Later, all six were dead of Kuru. The girl shows a left internal strabismus.

described by the natives in almost non-variant form throughout the Kuru-affected region; and both the disease and descriptions of its phases have become part of the traditional magic lore of the Fore people. However, in the following account we will emphasize the variations in the clinical picture we have been able to observe. Various aspects of the clinical picture of Kuru are illustrated in Figures 4 through 9.

The first symptom is locomotor ataxia, insidiously progressive and often noted by others before the patient himself is aware of it. About one-third of the patients report pains in the knee, headache, malaise, fever, cough or coryza, in order of decreasing frequency, as prodromal symptoms, but none report an acute incapacitating antecedent illness with emesis, stiff neck, convulsions, pareses, coma or even moderate interference with normal activities. None show signs of recent weight loss. Thus, antecedent acute infectious illness, severe enough to be recognized as meningoencephalitis or any other clinically diagnosible acute infectious disease, is absent.

The ataxia becomes more marked, with awkward placement of the feet and a swaying and weaving gait, and the patient tends to trip and stumble. He often describes this phase as "loose knees." If pain in the knee is reported associated with the onset, it rarely persists for more than a few weeks. As ataxia becomes progressively more severe, a distinctive tremor involving the trunk, extremities and head appears. This tremor is exaggerated when the patient attempts coordinated voluntary motor activities, is placed in any unstable posture, or when he is excited, apprehensive, fatigued or exhausted. Within one month of the onset both



FIG. 5. A female victim of Kuru dragged out of the native house to which she was already confined. Her husband and his second wife help support her. The others in the picture are all children of the patient. This patient died one month later.

the ataxia and tremors are usually prominent but the patient generally continues a normally active life.

The tremor is usually of fine quality, irregular but approximately of 2 to 3 per second frequency and has the appearance of shivering. It largely subsides when the patient is sitting quietly and is relaxed, and it disappears in sleep. Generally tremors appear when the patient is emotionally stimulated and they become exaggerated upon muscular activity, particularly in those muscle groups placed under controlled motor response or required to maintain unstable posture. During the second to third month of illness, when tremors become more severe and rather coarse in quality, they may interfere with eating and with any fine motor skills involving hands or feet. A choreiform component may enter into the involuntary motor pattern. Some patients progress to wild, somewhat athetoid involuntary movements in addition to the tremors and choreiform jerks; this is particularly noticeable when they try to arise to an erect position from a recumbent or sitting posture. By this stage the patient is no longer able to walk without the support of a stick; yet he generally continues to perform his usual daily chores about the village and gardens. Most patients, however, can continue to walk with such support for only one or two months; thereafter they can no longer maintain their equilibrium unassisted. From that time on the patient remains sedentary but still moderately well integrated in his native society, sitting outside the house and half-carried to attend pig feasts or other social functions. However, he invariably deteriorates rapidly until he can no longer balance himself, not even in a sitting posture,



FIG. 6. A, Fore Kuru victim with her husband; the patient delivered a normal infant one month later and her illness rapidly progressed to terminal stages during the ensuing four months. B, a middle-aged Fore woman with Kuru who extends her hands cautiously for support in dropping to a sitting posture.

without being supported and thereafter is carried out of the low, dark kunai-grass house only for urination and defecation. In a short while, in this advanced stage of disease, reached in the usual village setting at generally from three to six months from the onset, the patient is no longer carried from the dark house but left to lie indoors with fecal and urinary incontinence and rapidly developing decubitus ulcerations. Convergent strabismus is often present at this time. Until the patient can no longer maintain a sitting posture unaided, he usually can still bring food to his mouth and eat; but once he assumes decubitus he must be fed. This stage is brief, however, and the mute patient then rapidly succumbs to starvation, infected decubitus ulcerations, occasional accidental burns from the house fire, and secondary static bronchopneumonia. During this entire course the patient remains afebrile unless fever accompanies a transient intercurrent infection.

Speech and intelligence are normal in the early stages of the disease, but dysarthria appears in the second to fourth month and becomes more marked as the disease progresses. By the time the patient is no longer able to walk without extensive bilateral support, speech is usually extremely blurred and slurred yet it is still intelligible, and verbal responses, although much slowed, reveal good orientation and are usually appropriate. Even at an advanced stage of incapacitation the mute patient, who only occasionally groans, may still behave intelligently to requests with a feeble motor response after much verbal urging.

As the disease progresses, but still in the early



FIG. 7. A, a middle-aged Fore Kuru victim who braces herself with both arms to maintain equilibrium while sitting. B, a young Fore woman no longer able to maintain sitting posture without support. An aide restrains her head to control tremor for photography. A marked internal strabismus has developed.

months of illness, a marked emotionalism appears with inappropriate excessive laughter and slowly relaxed smile or paroxysmal hilarity alternating at times with moods of depression and, occasionally, of moderately belligerant and aggressive behavior. This moodiness, more usually that of excessive euphoria than of depression, settles later into a gradual pattern of withdrawal with an immobile facies, less mask-like than that of classic parkinsonism, often present and with a flexed posture characteristic of the disease. In those few patients who are adult males, a dejected, somewhat morose and somber facies is usual, whereas the usual patients—children and women—tend to be happy, even euphoric, in mood and appearance. In the native village the disease usually runs its course in six to nine months and rarely lasts over one year. Occasionally patients die within three to six months of the onset. A few cases, particularly in older women, run a more slowly progressive course to death in one to two years or longer.

Thus far in fourteen of our first 200 studied cases recovery has apparently occurred. Of these, we have only studied and examined six patients actually during attacks of Kuru and for the other eight we have accepted what appears to be reliable anamnestic data to the effect that they have recently had typical early Kuru which has subsided. Of the six fully examined patients, now apparently recovered, only three were considered unquestionable Kuru cases when we first examined them. In the remaining three the ataxia and tremors have been so mild or early that we have always been in doubt about accepting the native diagnosis in these cases. The three patients with moderately advanced cases, however, had marked ataxia, incoordination, tremors and emotionalism characteristic of moderately severe Kuru; we must concede that these are instances of observed Kuru "recoveries." All three were adults of somewhat hysterical temperament: two women and one young man. It is our current hypothesis that the illness is uniformly fatal and that the recoveries that we have documented and the six we have observed are cases of hysterical mimicry of the ataxia and the dramatic involuntary tremors and incoordination of Kuru. Since the Kuru pattern occupies a very significant place in current Fore

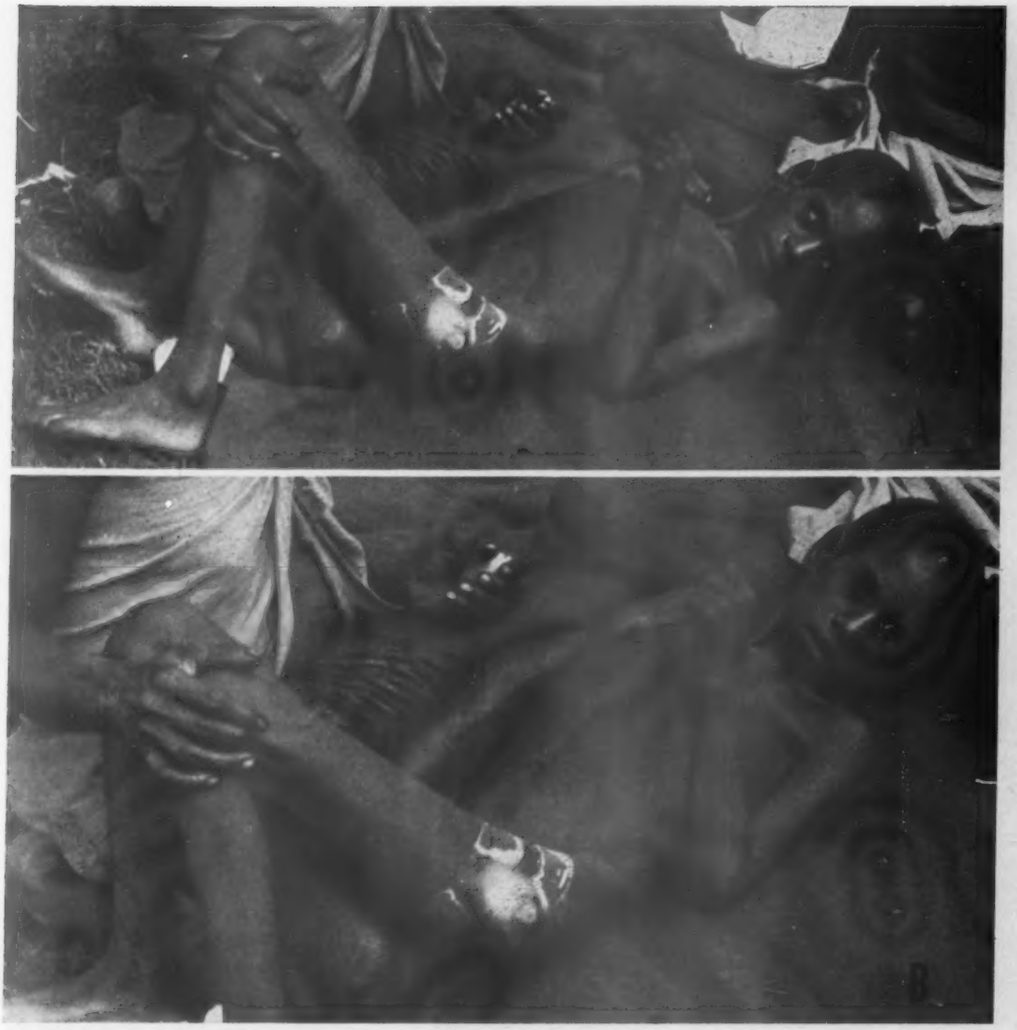


FIG. 8. A Fore boy in the terminal stages of Kuru with large decubitus ulcers. A, lateral deviation of the eyes is unimpaired. B, a few seconds later, marked left internal strabismus is evident on forward gaze.

culture, as already indicated, it would not be surprising to find it a pattern for occasional hysterical mimicry. In this connection it is of interest to note that R. M. Berndt has described an hysterical shivering and shaking occurring in men, women and children as a manifestation of a "cargo" movement in certain linguistic groups in the New Guinea Highlands [*4*].

The course of the disease is usually unrelentingly progressive, with continuous and uninterrupted deterioration. However, a rare case with remissions and exacerbations has been recorded. One woman gave a history, verified by interviews with others in her village, of having had typical early Kuru some fifteen to seventeen years before which lasted several months after the delivery of her first child and then subsided. Again, some twelve or fourteen years ago, just after the birth of her second child, she had Kuru with complete remission after a few months of mild tremors and ataxia, and now, for a third time, just after the birth of her sixth child, Kuru has developed. This third attack is a typical case of moderately advanced Kuru now in its third month of progression, and showing no signs suggestive of remission. A second, moderately severe case in a woman of twenty-five years is reported to be in its third exacerbation, having completely remitted twice (once fifteen or eighteen months ago and a second time six months ago) for periods of several months after having progressed to the stage of such tremors



FIG. 9. A, a Fore girl with early Kuru whose head tremors are restrained by her father. B, the same child several months later, mute and no longer able to stand or sit.

and ataxia that a stick was required for walking. The latter case appears now to be rapidly advancing and we believe it will soon be fatal.

In addition to these rare recoveries and remissions we have found two atypical cases of Kuru which are already of several years' duration and which appear and remit with the onset and termination of the patients' menstrual periods. Whether this periodic non-malignant illness and the cases of apparent recovery are examples of Kuru incompletely expressed—*formes frustes* of Kuru—which may offer valuable clues to its pathogenesis, or whether they are distinct nosological entities remains an unsolved problem.

Kuru does not interfere with normal pregnancy. Many of our patients with Kuru are pregnant; four have delivered normal children while suffering from moderately advanced disease. We have recorded many cases of normal pregnancies and of deliveries of normal infants even in very advanced and incapacitating stages of the disease. Other patients have died before term without miscarrying before death. However, when a mother dies of Kuru leaving a small suckling infant, the child frequently dies of malnutrition since no other nursing woman takes over care of the infant.

Pregnancy may have a significant effect on the progression of Kuru. Thus, we have frequently noted that our patients with Kuru are often pregnant mothers, or mothers with young nursing infants, and that during their pregnancy the illness is usually static, their condition tending to deteriorate rapidly during the few months after

parturition, while they are nursing. This situation has not been investigated critically enough to have been unquestionably verified, but it is a phenomenon sufficiently frequent to have attracted our attention over the past year of observation of Kuru cases.

A remarkable aspect of Kuru as it is met with in the native communities is the extraordinary fatalistic attitude with which the patients and, in general, their relatives accept the disease. Patients know they are to die; they have observed the terminal incapacitating stages of the disease in others, and yet discuss the matter of their advancing illness freely and without apparent anxiety. They will laugh at their own stumbling gait and falls, their clumsiness, their inability to get food into their mouths, and their exaggerated involuntary movements, and kinsmen will join them. The family members live with the dying patient, siblings sleep closely huddled to their brother or sister in decubitus, parents sleep with their Kuru-incapacitated child cuddled to them, and a husband will patiently lie beside his terminal, uncommunicative, incontinent, foul-smelling spouse. They may abandon at an early stage such supportive measures as feeding and washing and bringing the patient out into the sunlight, but they never cease to give strong emotional support and security to the patient who, as have they, has accepted the inevitable fact of impending death since the onset of the illness with equanimity. Thus the emotionalism and euphoria of Kuru is supplemented by a security engendered from certain knowledge that one is accepted by his villagers as an unfortunate victim of Kuru sorcery whom they will not desert before death claims him. The vengeful search for the offending sorcerer, which is often the primary concern of the patients' kinsmen, is a source of further emotional support.

PHYSICAL FINDINGS

In early stages of Kuru physical examination reveals no systemic abnormalities other than those referable to the central nervous system. There is no fever except for that associated with inevitable occasional intercurrent infections. Nutrition is generally excellent and there is no muscular atrophy. The cardiovascular, respiratory, gastrointestinal, hematopoietic, genitourinary and endocrine systems are normal. Examination of the abdomen reveals no abnormalities and there is no hepatomegaly or splenomegaly. There is no lymphadenopathy. The skin and mucosa are clear; there is no enanthem or exanthem. No heavy metal lines or abnormal pigmentation are seen on the gums or buccal mucosa except for the bluish grey plaques opposite the line of dental occlusion seen in most natives of this region. Until late in the illness there is no muscular weakness or paralysis and no rigidity or spasm. Although in advanced stages severe but inconstant muscular spasm and intermittent resistance to passive motion of the extremities appears, muscular contractures are very late in developing in spite of the predominantly flexed posture which the patients generally assume. In the terminal stages muscular atrophy becomes pronounced and some paresis or paralysis may develop.

The earliest sign of the disease is the slight ataxia often noted by the patient or his villagers before we are able to convince ourselves of its existence. The tremors, next to appear, are characteristic in that they appear to be closely associated with those muscle groups called upon to maintain any given posture against gravity. Thus, the muscles of feet and legs especially show exaggeration of this tremor when the patient is trying to execute a Romberg test or to stand on one foot. When executing finger to nose tests, excessive tremors of the outstretched arm and hand are evident and these persist until the finger comes to rest on the nose or face where it is stabilized and supported. In the finger to finger test some patients actually link the opposing index fingers together or press the fingers firmly together when they meet to control these tremors. The tremors can be considerably minimized or even occasionally completely abolished by supporting the trembling patient with firm and extensive antigravity support. Thus, one small boy with Kuru, who trembled violently when trying to sit or stand alone, had discovered a means of almost completely controlling his involuntary movements by remaining inactive in a flexed, fetal posture cuddled closely into his mother's lap. His responsive mother held him thus completely supported throughout the day. His Kuru tremors would only appear when he was removed from this extensive maternal antigravity support.

Sensory examination appears normal. Although few patients have cooperated sufficiently through the barrier of language and culture which we have slowly managed to surmount, we have found light touch, temperature, pain,

vibration, two-point, and position sense normal in a sufficient number of our moderately severe patients to convince ourselves that disturbances in sensation do not exist, at least in the first few months of the disease. Examination of the eyes reveals no abnormalities other than a convergent strabismus which most often first appears late in the illness; in a few cases it occurs in the early stages of the disease. Vision is normal. Extraocular movements retain their normal range even when marked strabismus develops. When severe tremors are present, the patient has difficulty in maintaining a fixed gaze and his glance tends to shift about rapidly and irregularly. True nystagmus is absent but irregular nystagmoid jerking of the eyes is the rule. The pupils react normally to light and to accommodation. Blinking frequency is diminished in many patients. Funduscopy reveals no papilledema, exudate or hemorrhages, optic atrophy or macular degeneration or other abnormality. There is no greenish yellow pigmentation at the sclerocorneal border (Kayser-Fleischer rings). Certain patients who are already sedentary and who remain indoors in the dark huts show a peculiar twitching, clonic movement of the eyelids and eyebrows when they try to keep their eyes open in the light outdoors. Rarely a patient with an advanced case shows a unilateral partial ptosis.

Cranial nerve functions remain intact, except for those disturbances referable to the incoordination and generalized disordered tone (i.e., strabismus, ocular ataxia, dysarthria, dysphagia). Hearing remains normal. Emotionalism and intellectual slowing have already been mentioned, together with the progressive dysarthria. Slight disturbances in articulation may appear while the patient is still ambulatory, but marked dysarthria, and, later, dysphagia are present in all advanced cases. The tongue is protruded and deviated normally and shows no fibrillation or tremors, but if carefully observed in the later stages of the illness, quick shock-like jerking movements of the protruded tongue are noted. In late stages of the disease drooling of saliva is common and some patients appear to have considerable difficulty in opening their mouths or protruding their tongues, as also, in such advanced disease, in directing and focusing their gaze. In such patients it is impossible to perform an adequate sensory examination or to evaluate fully their state of awareness and orientation.

The pattern of deep tendon reflexes and of cutaneous reflexes remains normal in most patients, although some patients reveal moderately hypoactive responses and others moderately hyperactive reflexes. Often, particularly in advanced disease, an unsustained but 5-to-10 times repetitive ankle clonus is found—and, more rarely, a sustained clonus—sometimes accompanied by unsustained patellar clonus. Normal deep tendon jerks usually pass to hyperactive responses and then become hypoactive in the terminal stages. In the stage of hyperactive responses a repetitive ankle and knee jerk and a pectoralis after-tremor are noted. Abdominal reflexes frequently disappear as the illness advances. Cremasteric reflexes in male patients remain active. No other reflex abnormalities are usually seen. Signs of damage to the pyramidal tract may be absent until late in the disease and plantar responses are usually flexor in type even in the terminal stages of the illness, although occasionally, extensor plantar responses, often transient, are obtained in advanced cases.

Cerebellar function tests reveal that the Romberg sign is present after the disease has progressed for a few months; but earlier we have noted that the patients first lose the ability to stand on one foot with eyes closed, and subsequently they cannot maintain balance on one foot even with their eyes open. Cerebellar function tests tend to exaggerate the irregular tremors and choreiform component in the involuntary jerks; at times even a somewhat athetoid pattern appears in the extremities of patients attempting these tests in the more advanced stages of the disease. Usually the response to the heel-shin test is more extensively disturbed than are the responses to the finger-to-finger and finger-to-nose tests, and difficulty with the heel-shin test tends to appear earlier than that in the upper extremities. This difficulty includes a wide amplitude tremor of foot and leg in attempting to place the heel on the tibial tuberosity, difficulty in initiating and in maintaining continuous smooth progression of the heel down the shin, and slipping of the heel from the shin with sudden overcompensatory clonic jerking of the leg as such slipping occurs.

When standing with feet together, the patient with early Kuru demonstrates postural instability with, in addition to exaggerated tremors, characteristic clawing and gripping movements of the toes, which tend to dig into the ground for

support. In patients with moderately advanced disease, no longer ambulatory, we have occasionally noted a remarkable sustained patellar clonus elicited by only raising them to partial weight bearing on their own legs; a few ambulatory patients show a shifting, unsustained patellar clonus as they stand trying to maintain balance. Adiadochokinesis is present in early Kuru, and "piano-playing" and other fine finger movements, rapid clapping and rapid alternating pronation and supination soon become slow and deliberate and later very awkward and clumsy.

LABORATORY FINDINGS

Laboratory examinations have thus far revealed little departure from normal. Lumbar punctures with check on cerebrospinal fluid (CSF) dynamics and CSF examinations, repeated hematological examinations and urinalyses, numerous clinical chemical determinations and serological studies have been made in over eighty-five of our 200 cases of Kuru. These have included studies in twenty-eight children under fifteen years of age. Hematological studies have regularly included erythrocyte and leukocyte counts and differential leukocyte counts from stained thin films, hemoglobin determinations (Sahli), and Westergren erythrocyte sedimentation rates. Urinalyses have included pH and specific gravity, sugar and albumin determinations and microscopic examinations of urinary sediment and a test for bile. Cerebrospinal fluid examinations included cell counts and Pandy tests, total protein, sugar and chloride determinations, colloidal gold reactions and Wassermann reactions (both warm and ice box methods). The results of all of these routine studies have, in general, remained within normal limits with the few exceptions to be discussed. In particular, no CSF pleocytosis has been found in any patient, not even in those near death, and no elevation in CSF protein has been detected. A few patients have given weakly positive syphilitic serology and syphilitic-type colloidal gold reactions without associated CSF pleocytosis or protein elevation. We have been unable to interpret these rare aberrant reactions. Spinal fluid pressures and dynamics are normal. Patients tend to have 5 to 10 per cent eosinophilia, occasionally 10 to 20 per cent, but this is apparently not strikingly different from the normal Fore populace. Sedimentation rates are usually normal, although a few elevated sedimentation rates have been encountered which we could not account for by any detectable intercurrent infection, pregnancy, or other cause. The results of liver function tests on over fifty of the patients have been normal as have blood urea nitrogen determinations.

Serum protein determinations (total serum proteins and serum albumin, total serum globulin, serum gamma globulin) have revealed unusual serum globulin patterns which are, however, characteristic of the serum from many New Guinea Highland natives not suffering from Kuru. Paper electrophoretic studies of serums and of hemoglobins from our patients have been performed by Dr. Cyril Curtain of the Baker Institute in Melbourne. Enormous elevations of beta globulins in many cases, and high alpha globulin levels in some have been encountered. These have been substantiated by electrophoretic studies in the Tiselius apparatus. These findings must be correlated with results in normal Fore natives, and this matter is under investigation. Paper electrophoretic study of the hemoglobins from patients with Kuru has revealed no abnormal hemoglobins.

Autoimmune complement fixation tests (AICF reactions) [*5,6*], carried out with normal human liver, kidney and brain tissue antigens, have failed to reveal any high-titer positive reactions.

Blood group testing of over 100 patients with Kuru for A-B-O, MN-S, Rh, C^w, P, Le^a, and $F_y{}^a$ and K systems by R. T. Simmons of the Commonwealth Serum Laboratories in Melbourne has revealed a pattern similar to that reported for natives of Chimbu, Nondugl and Mt. Hagen in Central Highlands of New Guinea [*7–9*]. A smaller number of specimens from Kuru patients has been tested for Wt^a (Wright) and Di^a (Diego) groups and, like the results for other New Guinea populaces [*10*], no positive reactions have yet been encountered. Serum titers for anti-A and anti-B were all normal and search for atypical blood group serum antibodies revealed none. At the present time we are conducting with Dr. Simmons extensive blood group genetic surveys of the Fore, Kimi, Keiagana people in the Kuru region in order to compare the results of Kuru patients with those of the normal, Kuru-free populace. In addition, similar studies are being made on entirely Kuru-free Auiana, Yar and Kukukuku populaces surrounding the Kuru region.

Serum and total blood copper and manganese

levels, together with estimations of other trace metals in blood, urine, CSF, and in tissue specimens obtained at autopsy are being determined. No abnormalities have yet been discovered. In particular, an exploratory spectrographic survey of ashed urine and blood samples and of tissue specimens obtained at autopsy and collected in trace metal free containers have been carried out by A. Walsh and B. Russell at the Chemical Physics Section of the Division of Industrial Chemistry of the C.S.I.R.O. (Commonwealth Scientific and Industrial Research Organization of Australia). Such qualitative spectrographic analyses should have detected any heavy metal present in significant quantity in the specimens; instead, the analyses indicated the absence of any unusual or toxic metals. Sixteen blood specimens from Kuru patients and seven blood specimens from normal Fore control subjects have revealed the following specific elements, with no differences in metal composition between Kuru patients and control subjects: iron, magnesium, calcium, sodium, potassium, aluminum and copper. Three specimens of blood from Kuru patients showed spectrographic evidence of manganese in addition. Specimens of liver, psoas muscle, kidney, bile and spleen from two subjects with Kuru have revealed only the same elements with traces of manganese in kidney, spleen and liver and of zinc in kidney and liver. Eleven urine specimens from Kuru patients, seven of which were collected several hours after injection of high doses of BAL (dimercaprol), have revealed only the same elements present in the blood specimens, while two specimens have also contained traces of manganese. Quantitative (atomic) absorption analyses for copper in 11 ashed blood samples from Kuru patients and 6 ashed blood specimens from normal Fore control subjects failed to reveal any significant differences in the copper content of blood from control subjects and from Kuru patients. Similarly, additional blood copper estimations performed by Mr. Baseden and Mr. Southern, soil chemists of the Department of Agriculture in Port Moresby, Papua, have revealed normal or slightly elevated blood copper levels in a number of Kuru patients, but no more elevated than such levels in control Fore subjects. Manganese determinations have not yet been completed.

Serological survey for neutralizing antibodies to known encephalitic viruses will later be made on the large serum file of serial serum specimens from our patients which has been accumulated. Thus far, only estimations of neutralizing antibody to Murray Valley encephalitis virus, which, with the exception of dengue, is the only arthropod-borne encephalitic virus so far isolated in New Guinea or Papua [*11*], have been completed. These yielded negative results. They were performed by Dr. S. G. Anderson at the Walter and Eliza Hall Institute in Melbourne, Australia.

Studies on the streptococcal flora in the nasopharynx of Kuru patients (in collaboration with Dr. Margaret Holmes of Melbourne), of antistroptolysin titers, of urine amino acids, and other biochemical and microbiological investigations are not yet completed and will be reported elsewhere.

PATHOLOGICAL FINDINGS

During the year of intense field study of Kuru twenty-nine autopsies were performed on patients belonging to the series of over 350 cases of typical Kuru which were under investigation. Autopsies were performed at the Kuru Research Center of the Okapa Patrol Post in all but two instances (Cases 19 and 22) which were performed at the Kainantu Hospital where the patients were brought to remove them from all contact with food and water of the Kuru region. Visceral tissues were fixed in 5 to 10 per cent formal-saline and Zenker's acetic acid. Brains and spinal cords were fixed by suspension in 5 to 15 per cent formal-saline and allowed to harden for about six weeks before being shipped by air to Australia or America. Table 1 summarizes all autopsy specimens that have thus far been obtained from Kuru patients, and where and with whom the brains of these patients have been deposited for study. In each case the entire brain including the upper cervical spinal cord was removed. In a few of the later cases the entire spinal cord including the cauda equina was taken. Eyes were taken from only five patients. Visceral specimens include all abdominal and thoracic viscera, and all endocrine glands including the pituitary, specimens of muscle and bone, fascia, peripheral nerves and vessels. Pathological studies on these specimens are in press [*11a,11b*] and complete case records on these cases will appear in a later publication.

No gross pathological lesions were found, notably none in the brain, meninges or liver. Microscopic study of formaldehyde and Zenker's fluid-fixed liver, spleen, kidney, heart, lungs,

TABLE 1

SUMMARY OF AUTOPSIES PERFORMED ON KURU VICTIMS

Case No.	Name	Sex	Age (yr.)	Village	Date of Autopsy	Location of Pathological Specimens*	Specimens Collected			
							Brain†	Complete Cord	Viscera	Eyes
1.	Kinao	F	5	Mage	5-16-57	Melbourne 1	+	0	+	0
2.	Yoei'a	F	45	Ibusa	5-24-57	N.I.H.	+	0	+	0
3.	Natameia	F	9	Wanitabi	6-18-57	N.I.H.	+	0	0	0
4.	Yaboiotu	F	50	Moke	6-27-57	N.I.H.	+	0	+	0
5.	Asomeia	F	25	Awante	7-6-57	Melbourne 1	+	0	+	0
6.	Inome	F	6	Wanitabi	7-8-57	N.I.H.	+	0	+	0
7.	Mulinapa	F	6	Wanitabi	7-13-57	N.I.H.	+	0	+	0
8.	Aranaka	M	7	Anumpa	7-15-57	N.I.H.	+	0	+	0
9.	Nene	F	50	Kagu	8-3-57	Melbourne 1	+	0	0	0
10.	Iamogi	M	17	Mugaiamuti	8-9-57	N.I.H.	+	0	+	0
11.	Aso	F	13	Emesa	8-11-57	N.I.H.	+	0	+	0
12.	Tasiko	F	6	Aga-Iagusa	8-19-57	N.I.H.	+TMF	0	+	0
13.	Atona	F	7	Anumpa	10-7-57	N.I.H.	+TMF	0	+	0
14.	Ereio	M	14	Ofafina	10-11-57	Melbourne 2	+	0	+	0
15.	Isoisi	F	6	Tamogavisa	10-16-57	N.I.H.	+TMF	0	+	0
16.	Waruye	M	8	Amora (Atigina)	11-14-57	N.I.H.	+TMF	0	+	0
17.	Inare	F	30	Etesena	11-30-57	N.I.H.	+	0	+	0
18.	Yani	M	5	Kamata	12-13-57	N.I.H.	+	0	+	0
19.	Auwatnefa	F	30	Kuana	12-16-57	Adelaide	+	+	+	0
20.	Nata	F	8	Miarasa	12-29-57	Adelaide	+	+	+	0
21.	Seribe	F	12	Mugaiamuti	12-29-57	Adelaide	+TMF	+	+	0
22.	Epai'a	M	35	Yafanagona	12-30-57	N.I.H.	+	+	+	0
23.	Asisi	M	11	Arewinipi	1-8-58	Adelaide	+	+	+	+
24.	Aoga	F	11	Keianosa	1-13-58	N.I.H.	+	+	+	+
25.	Wakabara	M	12	Miarasa	2-17-58	N.I.H.	+	+	+	+
26.	Ivisa	F	6	Miarasa	3-9-58	N.I.H. and Neustadt	+	+	0	0
27.	Kuti	F	45	Pusarasa	6-15-58	N.I.H. and Neustadt	+	+	0	+
28.	Akuna	M	8	Miarasa	6-21-58	N.I.H. and Neustadt	+	+	0	+
29.	Isuema	M	4½	Yasubi	6-26-58	N.I.H. and Neustadt	+	+	0	0

* The pathologists at the above locations working on Kuru are:

N.I.H.—Dr. Igor Klatzo, Department of Clinical Neuropathology, National Institute of Neurological Diseases and Blindness, National Institutes of Health, Bethesda, Maryland.

Melbourne 1—Dr. Graeme Robertson, Professor of Neurology, School of Medicine, University of Melbourne, Melbourne, Victoria.

Melbourne 2—Dr. Sidney Sunderland, Professor of Anatomy, School of Medicine, University of Melbourne, Melbourne, Victoria.

Adelaide—Dr. Malcolm Fowler, Pathologist, Adelaide Children's Hospital, Adelaide, S. Australia.

Neustadt—Professor Oscar Vogt, Director, Hirnforschunginstitut, Neustadt/Schwarzwald, West Germany.

† TMF—Fixed in trace metal-free formal saline.

lymph nodes, pituitary, pancreas, adrenal, thyroid, testes, ovaries, uterus, bladder, stomach, intestine, striated muscle, fascia and bone have revealed no distinctive histological lesions.

However, microscopic examination has revealed diffuse alterations within the central nervous system involving nerve cells, myelin sheaths and glia. The main pathological findings in the central nervous system are: (1) widespread neuronal degeneration, (2) myelin degeneration, (3) astroglia and microglia proliferation, (4) presence of plaque-like anisotropic bodies, and (5) occasional perivascular cuffings with mononuclear cells.

Neuronal degeneration is of non-specific character and is represented by chromatolysis, hyperchromasia, shrinkage, and various degrees of vacuolation of the cytoplasm. Neuronophagia of the dead cells is frequent. The cerebellum and extra-pyramidal system are most severely affected. There are also changes in the anterior horn cells, inferior olives, thalamus and pontine nuclei. In the cerebellum ballooning of the Purkinje cell axons (so-called "torpedos") is a common finding. In some cases neuronal abnormalities were so slight that only by careful screening of areas showing an intense astrocytic gliosis could they be detected. In other cases few viable cells were left in some of the neuronal groups such as the red nucleus.

Myelin degeneration is present in some cases of Kuru and most commonly involves pyramidal, spinocerebellar tracts, brachia conjunctiva and brachia pontis. It often appears to be of rather short duration since the myelin degeneration may be recognized only by counter-staining of myelin preparations for neutral fat.

Astroglial proliferation is usually very intense and corresponds roughly to areas of neuronal degeneration. However, astrocytic gliosis may also be extreme in the regions of minimal neuronal loss. Microglia proliferation is equally intense and is found in both degenerative grey and white matter. In addition to the usual ameboid forms of microglia, rosette formations and enormous rod cells in the cerebral cortex can be observed.

Plaque-like anisotropic bodies are found in the majority of Kuru cases. They resemble senile plaques in their staining properties and they average 20 to 60 microns in diameter. They are found frequently in the cerebellum, occasionally in the basal ganglia and the cerebral cortex. They are argentophilic and most clearly seen in Bielschowsky or Holmes preparations. The rather homogeneous center is usually surrounded by a delicately frayed peripheral zone. These bodies are strongly PAS-positive and stain only weakly with Congo red. With Sudan IV they occasionally exhibit orange coloration. Stained with cresyl-violet and viewed in polarized light, they reveal a colorful anisotropism. Their antemortem formation is evidenced by the rather regularly found microglia reaction around these structures. These peculiar anisotropic plaque-like bodies are found in the majority of cases, without correlation with the age of the patient or the intensity of pathological changes.

Perivascular cuffings with mostly lymphocytic elements are seen in some Kuru cases. They are usually found in the medulla, pons and basal ganglia. These cuffings are few and certainly not of a magnitude seen in an active encephalitic process.

The intensity of the degeneration of neurons and fibers and of glial proliferation varies from case to case as does the localization of their major impact on various structures. However, the basic pathological pattern described is encountered in all cases. The lesions are more diffuse than those found in the slightly similar diseases seen in Moroccan miners which, in some respects, resembles Kuru [*12*]. These pathological findings do not incriminate or strongly suggest any particular etiological factor, nor are they identical with those of any previously described neurological syndrome.

Portions of the brains in two cases of Kuru, obtained within a few hours of death and placed promptly in buffered glycerine, were shipped by air to Melbourne where Dr. S. G. Anderson conducted virus isolation attempts at the Walter and Eliza Hall Institute. No infectious agent was isolated from the brain pieces by chorioallantoic membrane inoculation of chick embryos or by passage intracerebrally in suckling and adult mice.

THERAPY

Patients in all stages of illness, particularly those in the early phases, have been given a variety of therapeutic regimens in an attempt to determine whether or not any of the drugs employed could influence the course of the disease. The administration of large doses of sulfadimidine, penicillin, streptomycin, chloramphenicol and Aureomycin® has been without effect. Large doses of fish liver oil, crude liver extract (administered parenterally), thiamin, other components of the vitamin B complex, folic acid, and many multivitamin preparations and therapeutic doses of ferrous sulfate and ferrous gluconate have been given without noticeable change in the patients' conditions. Other drugs which have been administered in full therapeutic doses for ample clinical trials include acetyl salicylic acid, dl-methionine, the antihistamines—Benadryl® (diphenhydramine hydrochloride) and Pyribenzamine,® the anti-

convulsants—phenobarbital, Dilantin Sodium® (sodium 5-5 diphenyl hydantoinate), and Tridione® (3,5,5-trimethyloxazolidine 2,4 dione); and hormones—adrenocorticotropin, cortisone acetate, delta-1-hydrocortisone, thyroxin, stilbestrol, testosterone propionate, methyl testosterone, and pregnant mares' serum gonadotropin. The disease has remained unchanged or deterioration has progressed while patients have received each of these. Intensive courses of BAL in the form of oily injection of dimercaprol similar to those regimens reported effective in hepatolenticular degeneration have been used without demonstrable effect on the disease [*13–20*].

DIFFERENTIAL DIAGNOSIS

Rare cases of recovery which may be due to hysterical mimicry of Kuru have already been discussed. The further possibility of *formes frustes* of the disease has been mentioned. The usual moderately advanced case of Kuru offers no diagnostic problem either to the Fore native or to the physician. Early cases reveal no abnormality on physical examination other than a slight ataxia and the mildest of tremors. The slight ataxia is often noted by the natives in daily life before we have been able to convince ourselves of its existence and the mild tremor of the early phases is indistinguishable from that of shivering from cold, fatigue or apprehension. Fatigue or exertion tends to bring out both tremor and ataxia and thus aids in early detection. A convenient test, we have found, is to assess the patient's ability to stand on one foot. In a mild case, in the first month or two of disease, the patient may be able to maintain equilibrium on one foot with eyes open but not with eyes closed, while in slightly more advanced cases the patient cannot balance on one foot for more than a few seconds even with eyes open.

Clinically the disease is closely akin to Wilson's hepatolenticular degeneration, but we have found no hepatic involvement in any of our cases, including sixteen examined at autopsy, and greenish yellow pigmentation is absent at the sclerocorneal border. The following must all be considered in the differential diagnosis: other heredofamilial neurological degenerations including the cerebellar and spinal ataxias, such as hereditary spinal and cerebellar ataxia (Friedreich's ataxia), hereditary cerebellar ataxia with spasticity (Marie's ataxia), olivocerebellar and olivopontocerebellar atrophy, and parenchymatous cerebellar degeneration, and particularly, heredodegenerative disorders of the corpus striatum involving the basal ganglia, putamen, lenticular nucleus and globus pallidus which include paralysis agitans (parkinsonism) and Huntington's corea. None of these other conditions has been seen in these New Guinea natives other than a congenital tremor of which we have seen four examples, one in a Fore man of about thirty years of age, the second in a pregnant Kanite woman of about thirty-five years, the third in an Auiana man about forty-five years of age, and the fourth in an elderly woman of the Usurufa linguistic group. These congenital, heredofamilial tremors were more regular than those of Kuru and unassociated with the profound disturbance of posture and balance or the dysarthria and emotionalism found in Kuru, and, of course, they had none of the rapidly progressive degenerative character of Kuru. The four natives with these congenital tremors are leading full and essentially normal lives in their native societies. Among the Fore this rather rare congenital illness is embedded in their tradition and is known by the name "tavaravain avie" (another term for "shivering") or by the name "kogaisa en avie." The latter designation means "possessed by kogaisa." "Kogaisa" is the name of a tall, broad leafed plant whose leaves tremble in a breeze in a manner suggestive of the tremors of this affliction. The Fore believe that a pregnant woman who breaks this plant is visited by a "dream man" and subsequently delivers a child suffering from this congenital tremor. The Auiana, among whom we have recorded several cases of this type of tremor, call it "kogaisantamba."

Sporadic cases of parkinsonism have been observed at Chimbu, Mt. Hagen, Lufa and at Goroka in Highland Indigines, but none could be confused with the rapidly progressive and fatal course of Kuru.

The still mysterious, etiologically unsolved encephalitis lethargica (Type A encephalitis, Von Economo's encephalitis, encephalitis epidemica) epidemic in Europe in the decade following 1916 led to a high incidence of postencephalitic parkinsonism. At times, the antecedent acute encephalitis is said to have produced only minor clinical manifestations. However, none of the many descriptions of this strange

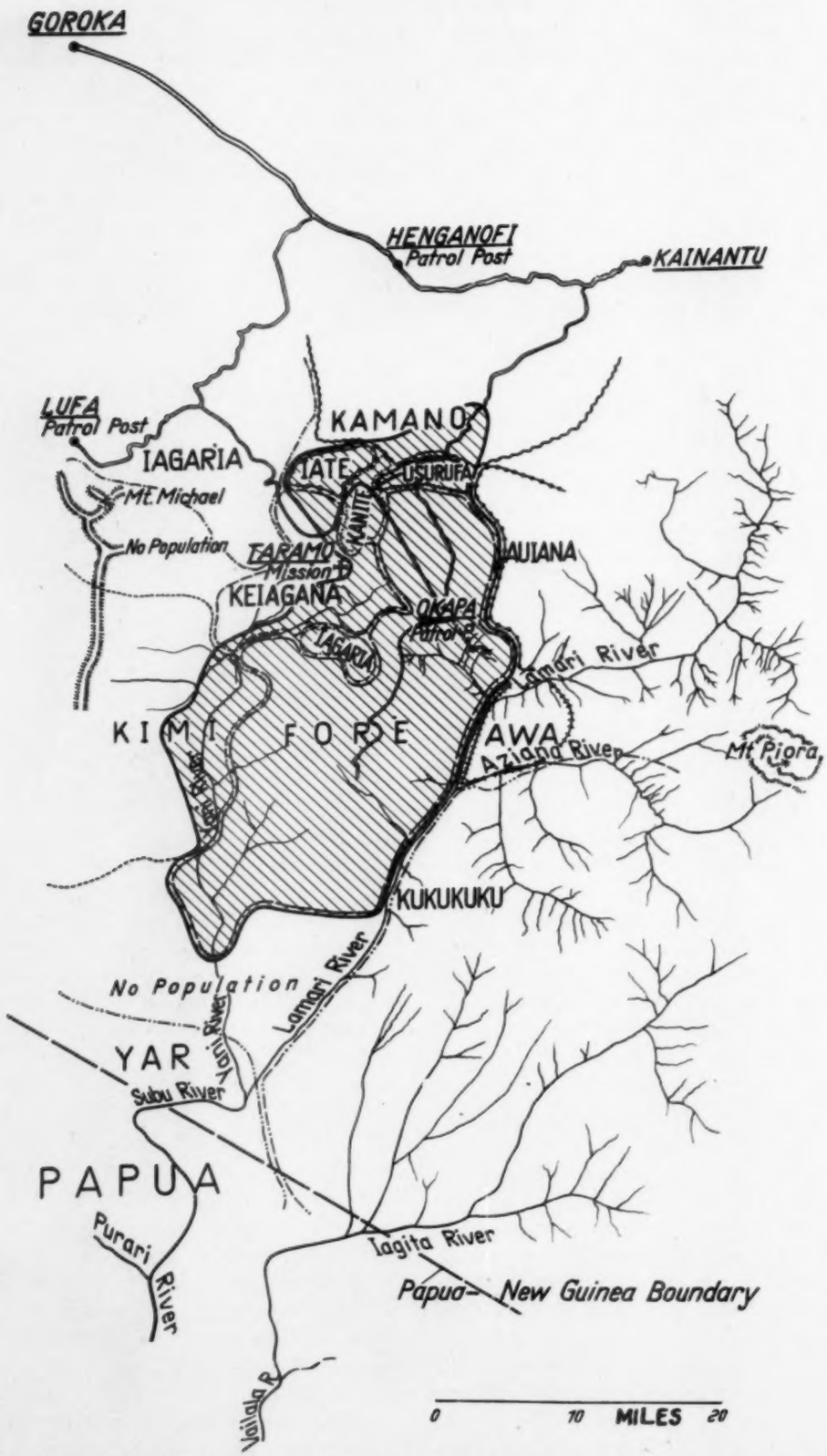


FIG. 10. The Kuru region of New Guinea, shown by hatching, is mapped with respect to the distribution of linguistic and cultural groups. ——— Kuru boundary. — — Papua-New Guinea boundary. ═══ Dirt surfaced road. ═══ Tracks only for four wheel drive. ——— Fore. – – – – Keiagana. ------ Kimi. —·—·— Iagaria (this group occupies a large region and an island between the Fore and the Keiagana groups). ——·····—— Yar. ——··—— Kukukuku. ++++++ Awa. ·-·-·-· Auiana. ~~~~ Usurufa. ····· Kanite. ○-○-○ Iate. ~~~~ Kamano.

illness (now disappeared) or of the more recent sporadic alleged cases thereof are consistent with the pattern of disease seen in Kuru. Furthermore, neurohistologic examination of our brain specimens have not disclosed any lesions similar to those described for this illness.

PROGNOSIS

Kuru, as already indicated, is usually an inexorably and rather rapidly progressive degenerative disorder of the central nervous system leading to total incapacitation in less than one year from its onset in the majority of patients. Early cases without strabismus, slurring or blurring of speech, or complete loss of equilibration may remit transiently or recover, or, rarely, periodically remit between menstrual periods. The problem of whether these rare cases are the same disease or some other syndrome has already been discussed. Once the patient is no longer able to walk, death in under a year seems inevitable, and no form of therapy which we have used has influenced the outcome.

EPIDEMIOLOGY

The total population of all the villages and hamlets afflicted with Kuru is about 17,000, some 11,000 of whom are the Fore people themselves. In this region we found and studied 200 active cases of Kuru during the first eight months of our Kuru Research Project. There were some 350 studied cases by mid-spring 1958. Of these patients over 200 have already died of Kuru. Another dozen patients are near death. We have by no means found every case in the region, although we believe we have found most of them. We estimate that some 150 to 175 cases of Kuru may currently exist in the region and that 1 per cent of the total population is at present afflicted with the disease and can be expected to die therefrom during the coming year. This is a conservative estimate. In certain Fore clans and tribes the present incidence of Kuru reaches 5 to 10 per cent of the population; and over the past five years over 50 per cent of all deaths in some of these communities have been from Kuru.

The extent of penetration of Kuru into the linguistic groups surrounding the Fore is illustrated in the accompanying map (Fig. 10) in which the Kuru region is shown on a much larger scale than in the previous map (Fig. 1) locating this area in New Guinea.

The disease is so strikingly clear and so dramatic in its symptomatology and course that valid histories of Kuru deaths in the past can easily be obtained. Interrogation of native informants, whose reports are verified by independent cross-checking, reveals that Kuru has been present for at least twenty-five years. A few well verified cases are said to have occurred twenty-five to thirty-five years ago. Old informants usually add that the illness was not present in their youth, but there is no way of assessing the reliability of such affirmations and we question strongly the validity of this contention. Until the current decade very little attempt to establish government control was exerted and until this year only two Caucasians have been resident in the entire region at one time. The first census among most clans was by government census patrols between 1951 and 1956. From notes in village census books over the past one to six years it is thus possible to verify a great many of the reported Kuru deaths. In most clans Kuru deaths are recalled before the first census patrol appeared. Thus, Kuru cannot be associated with the entry of Europeans into the region. However, intertribal trade routes may have introduced certain new crops and occasional manufactured items before European entry.

Age and Sex Incidence. Kuru is predominantly a disease of women. The age and sex distribution of the first 200 cases we have studied since March 14, 1957, is summarized in Table II, and the same data are presented graphically in Figure 11. It will be noted that 23.5 per cent (i.e., forty-seven) of our 200 cases occur in preadolescent or early adolescent children under fifteen years of age; the remainder are in older patients. Our youngest patients are two boys four to five years of age and we have recorded no history of a case of Kuru in a child under this age. There is a definite decreased incidence in early adolescence and a decided change in sex incidence with age. Of the forty-seven cases in children, thirty-four occurred in children under ten years while only thirteen were in children whose age was estimated at ten to fourteen years. All ages are, of course, estimated since the natives keep no track of age. Accuracy of estimation is increased in childhood and adolescence. At all ages but mid-to-late adolescence (fifteen to nineteen years) there is a predominance of cases in females, but among adults, who comprise over two-thirds of the cases, there is a striking female preponderance, with a male:female ratio of 1:7.8 among patients twenty to twenty-nine years of age. Only two cases of Kuru occurred in men among the ninety-three cases in patients whose age is estimated at thirty years of age or over. Since

TABLE II
AGE AND SEX DISTRIBUTION OF FIRST 200 STUDIED CASES OF KURU

Type of Case	5–9 Years		10–14 Years		15–19 Years		20–29 Years		30–39 Years		⩾ 40 Years		All Ages	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Studied in hospital	7	12	4	5	3	1	5	15	2	17	0	14	21	64
Fully examined in village	5	2	2	2	2	4	0	11	0	27	0	10	9	56
Not fully examined	0	8	0	0	4	2	0	13	0	13	0	10	4	46
Total by sex	12	22	6	7	9	7	5	39	2	57	0	34	34	166
Male: female ratio	1:1.83		1:1.17		1:0.78		1:7.8		1:28.5		.....		1:4.9	

more than two-thirds of the cases are in adults, the full impact of the disease is upon the young adult and middle-aged woman and it is evident that Kuru has been a major factor in producing the current male preponderance in the Fore population. One might speculate that the Fore pattern of early child marriage for girls—boys do not marry early—has been at least to some extent determined by the vulnerability of the child-bearing populace to Kuru.

ETIOLOGY

The Problem of the Possible Postinfectious Etiology of Kuru. We have been unable to elicit any consistent history of mild or severe antecedent illness which might be interpreted as an acute infectious disease. No seasonal variation in either time of onset or of death of Kuru patients has been detected. Among the Fore people and their neighbors there is no tradition or memory of any epidemic of encephalitic disease. During the ten months of Kuru investigation we have been supervising a regional hospital serving the 30,000 population censused from the Okapa Patrol Post and during this period we have observed epidemic pertussis, measles, chicken pox and epidemic parotitis. In addition we have seen epidemic upper respiratory infections, epidemic bronchopneumonia of infants and young children, and epidemic gastroenteritis of infants—these latter three conditions of undetermined etiology—and we have encountered eight cases of acute bacterial meningitis (with identification of N. intracellularis in four, D. pneumoniae in two, and H. influenzae in two).

Furthermore, during the past four months we have seen five cases of benign aseptic meningoencephalitis with transient cerebrospinal fluid pleocytosis of from 180 to 1,200 cells per cu. mm., 80 to 100 per cent of the cells being mononuclear. Such patients have been carefully studied. These cases have been in children in all but one instance, which occurred in a young adult female. The illness has more closely resembled benign aseptic (lymphocytic or mononuclear) meningoencephalitis than acute encephalitis for there have been no ocular symptoms and no somnolence, coma, convulsions, pareses or paralyses, and there has regularly been fever, malaise, irritability, severe anorrexia, headache and posterior neck pain and stiffness. All have recovered, although convalescence has been slow and the patients have been ill for more than one month before they could resume normal activity.

In two instances we have had two patients from the same village simultaneously ill with this syndrome. The etiology of these cases of meningocephalitis remains undetermined. They have not been associated with cases of mumps in their villages. No virus has been isolated from specimens of cerebrospinal fluid and of blood taken from three patients with acute cases and sent to Australia under refrigeration for animal and chick embryo inoculation. Acute and convalescent serum pairs have been collected from these five patients for examination for antibodies to those viruses and leptospiras known to produce this syndrome in man. Mumps has in this way been ruled out but other results are not yet available.

None of our patients with Kuru present a history of a similar illness antecedent to their Kuru and these five patients with meningoencephalitis have now recovered without sequellae. When these cases were shown to the kins-

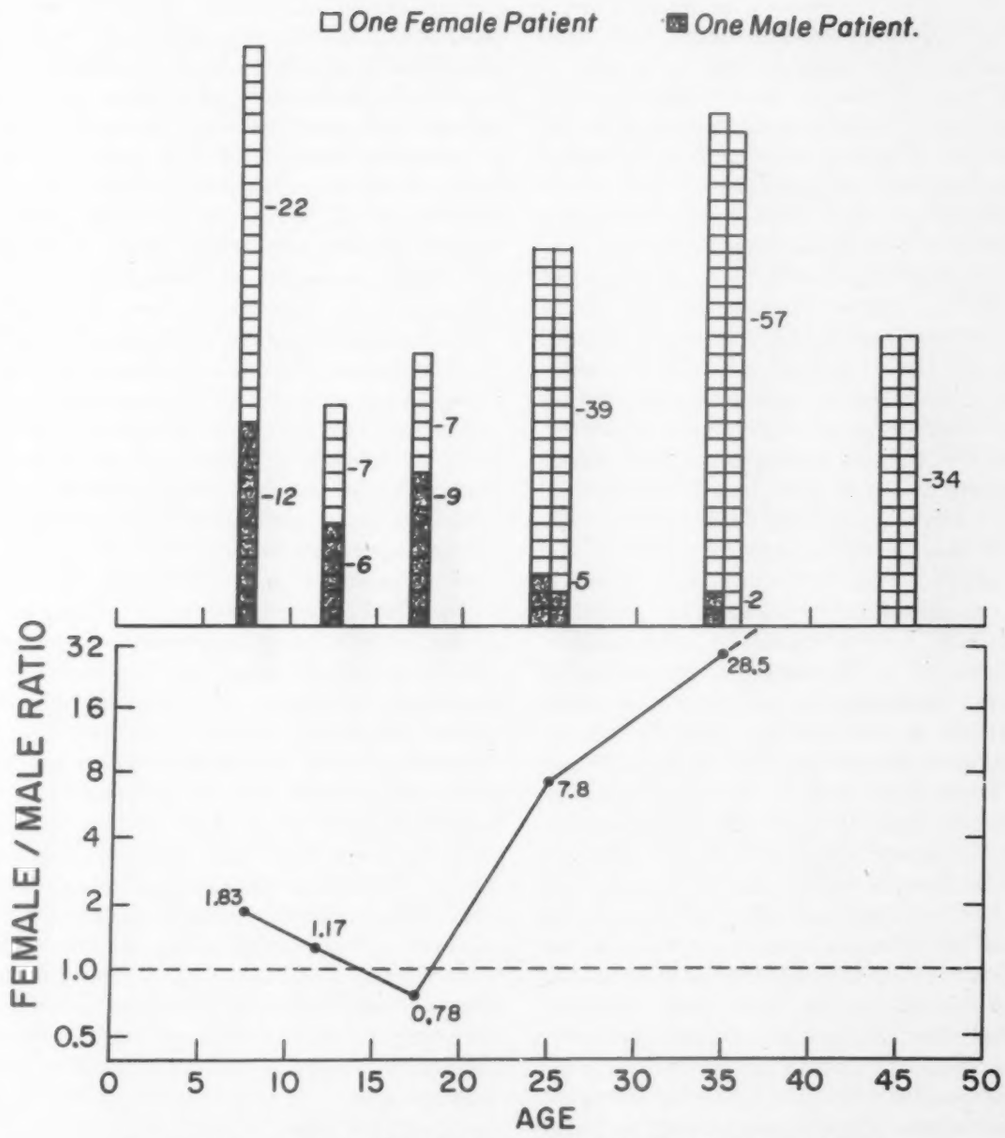


FIG. 11. Age and sex distribution of first two hundred studied cases of Kuru.

men of several Kuru patients and to the Kuru patients themselves they all denied that a similar illness had preceded the Kuru in the recent or remote past. Leprosy and yaws are less frequent among the Fore people than in many surrounding populaces who do not suffer from Kuru, and malaria is rare. Thus, we have observed no infectious disease which could readily be suspected as a possible regular antecedent to Kuru although many new cases of Kuru are constantly developing during our period of intense medical surveillance of the Kuru region. Furthermore, although about one-third of the patients with Kuru do report some headache and knee pains, and occasionally fever, cough and coryza antecedent to the insidiously appearing ataxia (the first sign of Kuru), we have not yet actually observed these symptoms in anyone who has progressed to clinical Kuru. Therefore, we must reluctantly conclude that Kuru is apparently not of postinfectious etiology.

The Problem of the Possible Toxic Etiology of Kuru. Kuru resembles in many respects Wilson's hepatolenticular degeneration in which recent research has demonstrated abnormalities in serum ceruloplasmin and copper transport and associated abnormal depositions of copper in the body [*22–33*]. The neurological manifestations of

chronic manganese poisoning [*12*], and, to a lesser extent, of chronic mercury and zinc poisoning, strongly suggest the symptoms of Kuru. In view of this we have made intensive search for possible heavy metal poisoning in our Kuru patients. Some of these studies were discussed under the section on Laboratory Findings. In collaboration with Miss Lucy Hamilton we have made extensive studies of the Fore diet, and the composition of soils, foods and of ashes from cooking fires and house fires in the Kuru region is being investigated. A search for all exposure to toxic agents including possible organic poisons as well as toxic heavy metals is in progress. Much further study of foods consumed, including the various fungi, grubs and insects eaten, the ashes used as "salt," and of methods of food preparation is required. Thus far, however, nothing in the Fore diet, or body painting, and no unusual pica has yet suggested a source of possible toxicity. We have found no abnormal metal content in blood or serum, cerebrospinal fluid, urine or in specimens of tissues obtained at postmortem examination. We have discovered no differences in the handling of foods or other raw materials between our Fore victims of Kuru and well members of their community or between Kuru-affected communities and neighbouring Kuru-free communities. Finally, the therapeutic use of repeated courses of BAL therapy in high doses has failed to influence the course of the disease, as has removal of the patients for many months from their native village environment to our Kuru Hospital, where their diet is supervised and supplemented with tinned meat and unpolished rice.

Animal nutritionists have had extensive experience with trace element poisonings and deficiency states of grazing animals on diverse types of pastures. It is tempting to draw a parallel between the localized pasture syndromes they have described and geographically localized Kuru. One specific pasture poisoning, the toxicity of Phalaris tuberosa, a perennial pasture grass, for sheep in Australia and New Zealand, strongly suggests Kuru. In sheep exposed to a phalaris-dominant pasture a staggers syndrome called "phalaris staggers" is produced and this neuromuscular disorder involving hyperexcitability, tremors, ataxia and incoordination, loss of ability to rise and progressing usually to death is in its clinical picture intriguingly akin to Kuru. It has been found that frequent oral administration of soluble cobalt salts to sheep will completely protect the animals against phalaris staggers even when they are grazed continually on pure stands of phalaris. Parenteral administration of cobalt and oral or parenteral administration of massive doses of vitamin B_{12} have no effect on either the development or course of phalaris staggers. Our studies of the grasses eaten by the Fore people as a vegetable and of other plants they consume and our epidemiological investigations of the Kuru pattern have failed, however, to suggest any parallel with this grass poisoning of animals [*34*].

The Problem of Possible Dietary Deficiency Underlying Kuru. No geological change has been noted in passing from Kuru to non-Kuru regions and the geological features of the Kuru region are so varied that it seems unlikely that some trace mineral deficiency such as of copper, manganese, molybdenum, cobalt or zinc, could exist in every hamlet in which Kuru occurs. Geological reconnaisance of the region has failed to reveal any link between the geology of the area and the occurrence of Kuru. The government geologist has described: " . . . a series of steeply dipping, faulted but barely metamorphosed sediments. These vary in grain size from mudstones to greywacke, grit and conglomerate. The greywacke contains, in places, fossil vegetable matter. Much of the coarser sediment is made up of volcanic material. Volcanic boulders up to 18 inches across occur in the conglomerate. The stones which are heated and shoved into the mumu pits for cooking are of various rock types including greywacke and grit, with constituents probably volcanic porphyry and ultrabasic igneous rock. Greywacke and grit often outcrop close to villages and igneous rocks occur in small dykes or in the conglomerate There is some limestone, and some siltstones in the region are calcic."

Extensive study of the Fore diet has revealed it to be superior in calories, in variety of foods consumed, and particularly in protein intake to that of many other New Guinea communities. No vitamin deficiency is found in the Fore diet, there is no endemic goiter in the region, and clinically detectable malnutrition of infants, toddlers and adults is exceedingly rare for a Melanesian community. Furthermore, the peculiar age and sex distribution of cases does not suggest a dietary, particularly not a mineral, deficiency, for exposure to trace elements in water and in soil and fire ash contamination of foods would not be less in men than in women

and children. On the contrary, pica for soil and contamination of foods with soil might conceivably be greater in women and children than among adult men (since women and children eat more often in the gardens), and thus produce a relative excess of some trace mineral in soil without it reaching truly toxic concentrations. Thus, an alternative theory of pathogenesis is suggested: It might conceivably be possible that excessive consumption of sulfate, molybdenum or some other trace mineral, for example—still at levels below those producing direct toxicity—by certain individuals of a race, all members of which are chronically deficient in some other essential trace metal (copper, for instance), might result in a relative deficiency state. Full elaboration of such a theory of pathogenesis would require further understanding of the interaction and intermediary metabolism of trace metals in man than we now possess and we have found no epidemiological nor laboratory data to support such a suggestion. However, in view of the interesting interrelations of molybdenum and sulfate in producing copper deficiency in sheep and cattle, which veterinary investigators have established [*35*], it is of interest to continue studies, as we are doing, in search of a possible direct mineral deficiency or an indirectly induced deficiency such as occurs in the molybdenum conditional hypocuprosis of cattle [*36*] or the "metabolic copper deficiency" induced by excess of sulfate and molybdenum described by Dick [*35*] in sheep.

Finally, our cases of Kuru first developing in Kuru-region natives after prolonged residence outside the Kuru region—one even after several months at a Papuan coastal plantation on a diet of rice and tinned meat with other supplements given coastal laborers—and progression of such cases to fatal termination without ever returning to the Kuru region require, if Kuru is the result of a deficiency state, that irreversible damage to the central nervous system occurs long before even the first subjective awareness of ataxia, since the neuronal degeneration progresses even if the deficient diet is discontinued. Our observation of relentless progression of the illness in our hospital-studied patients on a controlled diet further suggests this and makes an uncomplicated deficiency seem very unlikely.

The Evidence for Probable Genetic Predisposition as a Factor in Kuru Pathogenesis. In spite of complex kinship [*37*] and frequent child adoptions, a reliable enumeration of the pregnancies of any childbearing women can be obtained. The Fore are polygamous but tend to defend the marriage contract vigorously. Thus, assignment of paternity is probably no less certain than in many a literate community. Kuru deaths are found in the family history of well over one-half of our patients and in the parents or siblings of 46 per cent of the 200 study cases. In addition, certain families possess a striking history of Kuru, with several siblings, children of a mother who died of Kuru, developing the illness at different times but each at approximately the same age. Furthermore, we have many instances of the so-called law of anticipation, the illness developing in the children of an affected parent at an earlier age than in the parent although at a different time. In only one instance in our series, however, have a mother and child been ill simultaneously.

Villages and hamlets in the Kuru region range in population from a few dozen to several hundred inhabitants, the smaller hamlets predominating. Marriages within a single small group of hamlets have been the rule and marriage with close kinsmen has been preferred [*37*]. Thus, it would be difficult to find "control" families in the center of the Kuru region without a high incidence of the disease. However, although most persons in any group of associated villages are interrelated, it is still possible to compare immediate families of Kuru patients with those of normal natives. Such a comparison has recently been made by Robson, Rhodes and Bennett, who collaborated with us in the later months of the Kuru field study, in an analysis of geneologies from the villages of Moke, Kasogu, Anumpa, Keanosa, Etesena, Kasoru and Kagu in the northern part of the Kuru region [*38*]. They found that Kuru was given as the cause of death in about one-fourth of all reported deaths. Of 204 Kuru deaths, 177 were in females and twenty-seven in males. Of these, twenty-one females and nineteen males were classified as children under sixteen years of age. It is most impressive to note that these anamnestic data accord closely with those for our series of over 300 observed cases, and with the more extensive geneological data obtained during our epidemiological survey for recalled Kuru deaths throughout the Kuru region. Kuru occurred in 75 per cent of adult female offspring of women dying of Kuru and in 25 per cent of the female child offspring. The corresponding figures for female offspring of Fore women not dying of Kuru were 50 per cent for adults and 7 per cent

for girls. Male offspring of Kuru women showed a 25 per cent incidence of Kuru, while the incidence in male offspring of non-Kuru Fore mothers was only 1 per cent. These facts and findings that several children of both sexes are often involved when a parent (usually a mother) has died of the disease, are consistent with a one-gene hypothesis of transmission as a mendelian dominated trait with incomplete penetrance. According to such a hypothesis, the disease would occur in more malignant form in children in either sex in subjects homozygous for the Kuru autosomal gene. In the heterozygous condition, endocrine factors would apparently play an important role, permitting the expression of the disease only rarely in men and more regularly in women.

During extensive epidemiological investigations to establish the geographical limits and the pattern of Kuru incidence [*21*] we have patrolled over 1,000 miles on foot to almost every hamlet of the Kuru-affected region. On the borders between Kuru-affected and non-affected populations it has been possible to obtain histories of occasional, rare, sporadic cases of Kuru—often only a single individual case in a community—developing in otherwise Kuru-free populations. These cases have more often than not been in women who married into these Kuru-free communities from Kuru-affected areas. Furthermore, Kuru has often developed in these patients in the previously Kuru-free region after several months, or even years, of residence outside of their home Kuru-affected hamlets. In addition, we have now seen two cases of Kuru which have developed in men from Kuru-affected populaces while they were resident fully outside the Kuru region: one in a Kanite laborer to the Papuan coast in whom the first sign of Kuru developed two months after he started work on a Papuan coastal plantation; the other in a Fore prisoner on road work in a region north of the borders of known Kuru occurrence. Both men were on a rationed diet similar to that shared by all others working with him. We have documented other cases of very early Kuru in which the subject left entirely the Kuru-affected region with only minimal ataxia. Their disease has nevertheless progressed to further neurological deterioration and death. These instances tend to confirm our observation of relentless progression of Kuru in our hospital patients on a controlled diet and in those patients brought to the Kainantu hospital, where they are well outside the known limits of Kuru occurrence. Were it not for the much rarer but most confusing examples of Kuru developing in a few women from apparently low-Kuru incidence communities after entry into the Kuru region through marriage, the genetic basis for the malady would appear to be fully established.

Another item of evidence strongly suggesting genetic predisposition to Kuru lies in the history of the Wana clan of the Ke'efu-Hogeteru Tribe of Keiagana-speaking natives. This clan, on the border of the Kuru region, has experienced sporadic cases of Kuru for at least twenty-five years. It is closely related by marriage ties to other clans of the Ke'efu-Hogeteru tribe, closer to the Fore-Keiagana border, in which Kuru is even more frequent. About twenty years ago this clan was expelled by fighting from the Ke'efu region and sought refuge among the Kigupa tribe of Keiagana, a Kuru-free populace. The Kigupa people remained hostile to the intruders and did not intermarry with them. During two decades of residence in the Kigupa area the Wana clan had several of their women die of Kuru while the surrounding Kigupa People had no Kuru at all. Two years ago, inter-tribal fighting now largely at an end, the Wana clan returned to their traditional lands and the Kigupa clans have moved back onto the sites occupied by the Wana clan during their sojourn in Kigupa territory. On this ground Kuru has not occurred in the Kigupa natives, whereas the Wana clan has continued to experience Kuru cases, two new cases having developed among the 200 Wana natives since they returned to their traditional grounds in the Ke'efu, Kuru-affected region. In addition, Kuru has occurred in the past in the Kamano communities of Iababi and Onamuga, well outside of the boundaries of the Kuru area. It is of interest that these two Kamano communities are unusual in that they have had extensive Fore and Keiagana marriage contacts from the Kuru region during the period of inter-tribal warfare and many of their Kuru cases can be traced directly to Kuru-region women who have lived among them.

The etiology of Kuru therefore remains obscure. No aspect of nutrition or other feature of Fore culture has yet revealed any clue as to what environmental factors are operating in its pathogenesis. Genetic predisposition is strongly suggested by the type of clinical picture the disease presents, by the unusual age and sex

distribution of cases, by high familial incidence in a closely intermarried community, by the phenomenon of anticipation (with cases appearing at an earlier age in the second generation), by occasional geneologies wherein several siblings have died of the disease on reaching approximately the same age, and by the pattern of apparent introduction of Kuru through marriage into communities of low Kuru incidence on the Kuru-non-Kuru boundary. The historical episode of the Kuru-affected Wana clan bringing Kuru with them into a Kuru-free region where they fled for refuge during the period of intertribal fighting, but neither intermarrying with the surrounding Kuru-free populace nor leaving Kuru behind when they departed, is further evidence for genetic predisposition. Finally, the cases of Kuru developing in men and women from the Kuru region during residence well outside this region—in one case as far away and in as different an environment as the Papuan coast—all serve to limit the possibilities of toxic etiology. Thus, any toxic agent would have to be carried with them either as a cumulative poison stored in some tissues of the body and acquired by asymptomatic exposure long previously, or carried in the form of some toxic substance which they take with them from their home communities—any such substance we have been unable to identify. That they find in the new and strange environments a poison unknown to the local populaces or to modern medicine seems highly unlikely. Should Kuru be a self-perpetuating autointoxication resulting from either a genetic defect which makes some ordinarily well tolerated substance in diet or metabolism toxic for the patients—such as tyrosine in phenylpyruvic oligophrenia or copper in hepatolenticular degeneration—it would not be surprising that our current technics of investigation have thus far failed to explain its pathogenesis. Neuropathological studies have failed to suggest any autoimmune mechanisms such as are presumed to be active in erythema multiforme exudativum (Stevens-Johnson syndrome), rheumatic fever, glomerulonephritis, disseminated lupus erythematosus, periarterities nodosa and multiple sclerosis, although this type of mechanism coupled with genetic predisposition to such autoaggressive phenomena would be an attractive explanation for the disease. Extensive studies of the Fore diet, exposure to possible toxic agents and search for possible infectious factors is continuing, but thus far we cannot escape the conclusion that strong genetic factors are operating in Kuru pathogenesis, probably in association with as yet undetermined ethnic-environmental variables.

SUMMARY

1. A clinical, pathological and epidemiological study has been made of 200 cases of a new neurological illness occurring in natives of the Fore linguistic and cultural group in the Eastern Highlands of New Guinea and in their immediate tribal neighbors who intermarry with them. This appears to be related to the group of heredofamilial progressive degenerative disorders of the central nervous system. Since the onset of investigations over 350 patients have now been studied.

2. Kuru causes the death of about 1 per cent of the affected population each year. In some communities the present incidence of Kuru reaches 5 to 10 per cent, and over 50 per cent of all deaths have been from Kuru in certain areas.

3. The disorder principally affects adult females, but almost one-quarter of the cases are in children of both sexes. Rarely, adult males are involved. The disease is generally fatal in six to nine months. The occurrence of mild, remitting forms of the disease is discussed.

4. The illness is apparently restricted to the Fore people, some 11,000 in number, and to only those portions of their tribal neighbors, the Auiana, Usurufa, Kanite, Iate, Keiagana, Kimi, Kamano and Iagaria, who are immediately adjacent to the Fore-Kuru region—an estimated additional population of 6,000.

5. Neurohistological examination of fifteen of the twenty-nine brains thus far obtained from Kuru patients has revealed a widespread neuronal degeneration, myelin degeneration and astroglial and microglial proliferation. The cerebellum and extrapyramidal system are most severely affected. There are also changes in the anterior horn cells, inferior olives, thalamus and pontine nuclei. In addition, plaque-like anistropic bodies resembling senile plaques are found in the cerebellum, sometimes in the basal ganglia and cerebral cortex. Occasional perivascular cuffings with mononuclear cells are found. Gross and microscopic pathological study of other tissues from twenty-four patients have thus far shown no specific lesions.

6. Acute meningoencephalitis, with a mononuclear pleocytosis in the cerebrospinal fluid, has been discovered in the region but it has

been impossible to establish any relationship between this infection, presumably viral, and Kuru.

7. No antecedent encephalitic or meningoencephalitic illness or any other acute infectious disease has been identified in the study of Kuru and no nutritional or toxic factor has been incriminated as of possible etiological significance in the disorder. If the degeneration of Kuru is a postinfectious phenomenon the antecedent illness must be so mild or subtle as to escape detection by the natives and ourselves.

8. A congenital, familial tremor which does not greatly interfere with a normal life in native society has been found and is easily differentiated from the rapidly progressive degeneration seen in Kuru.

9. Extensive search for toxic factors which might be of etiological significance in Kuru, in diet, water, pica, smoke, materials used in body painting and in native salt preparations and medicines has been unsuccessful. Toxic trace metals have not been found in analyses of tissues from Kuru patients. The fact that Kuru has developed in natives from the Kuru region after long residence in alien environment with Kuru-free populaces, far outside the Kuru region, markedly limits the toxic possibilities. The possibility of a genetically determined intoxication with substances normally present in diet or metabolism is discussed.

10. A genetic predisposition is strongly suggested and the evidence for it is summarized, but the ethnic-environmental variables that are operating in the pathogenesis of Kuru have not yet been determined.

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Seminar on Connective Tissue

Endocrine Control of Connective Tissue*

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THE chemical mediation of the effect of hormones on the tissues is incompletely known. It is generally realized that the chemical structure of the hormones may determine their actions on the peripheral target, stimulating or inhibiting cell functions. A hormone may act as an accelerator or depressor of enzyme systems, directly or indirectly. It may participate in the enzymic process itself and influence the synthesis of enzymes as well as the concentration of co-enzymes, activators or inhibitors. Passing from the blood stream to the connective tissue cells, the hormones may influence the permeability of the capillary wall, the intercellular substance of the connective tissue, the cell and nuclear membranes, or the membranes of the mitochondria. These boundaries separate areas containing different enzymes, and the constant influence of circulating hormones constitutes a means for continuous control of the metabolism and life of the tissues. These chemical actions may be reflected as submicroscopic or even microscopic changes.

CONNECTIVE TISSUE

Connective tissue is ubiquitous; an overwhelming part of the mammalian organism is made up of structures of mesenchymal origin. Compared to the mass of fibrils and ground substance, the cells which manufacture these components of the intercellular material make up only a minute fraction of the total connective tissue.

Fibroblasts are known to be the sites of origin of collagen. The pre-stages of collagen are produced in these cells and are then liberated to the extracellular compartment where the molecules become oriented to form collagenous fibrils. There is some evidence that this orientation may take place in the cytoplasm. Analogous cells in cartilage and bone are the chondrocytes and osteocytes.

Mast cells are characterized by their cytoplasmic granules containing acid mucopolysaccharides which take a metachromatic stain with various basic dyes, e.g. toluidine blue. The acid mucopolysaccharides seem to occur in various degrees of polymerisation and in various degrees of sulfation, occurring even as non-sulfated mucopolysaccharide of the hyaluronic acid type. In addition, mast cells contain histamine and, in certain species, serotonin (5-hydroxytryptamine). Taken together, the mast cells in the mammal constitute a mass larger than the liver. In perivascular areas of fibrillar connective tissue, undifferentiated mesenchymal cells are generally indistinguishable from fibroblasts. Immature mast cells undoubtedly have their place among these.

Reticuloendothelial cells are mesenchymal cells present in loose connective tissue, in the spleen, liver and bone marrow. These cells possess phagocytizing and antibody-producing properties, thus participating in the defense mechanism of the body.

Ground Substance. In the loose connective tissue the formed elements are embedded in a gelatinous ground substance. Even within the firm collagen fibril bundles each individual component is ensheathed by ground substance. The chemical constitution of the ground substance varies, being different in loose connective tissue and in cartilage and bone. In cartilage the sulfomucopolysaccharide, chondroitin sulfate, predominates. The ground substance of fibrillar connective tissue as well as the fluids of mesenchymal origin contained in the cavities of the joints, the eye ball, the inner ear and the ovarian follicles contain water and salts, acid mucopolysaccharides and a variety of proteins and neutral

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sugars. Most of these constituents are supplied by the blood, whereas the mucopolysaccharides are formed by the local connective tissue cells. Hyaluronic acid is the only mucopolysaccharide known to be present in the synovia, as well as in the humors of the eye and the labyrinth. In the follicular fluid, however, chondroitin sulfate is present in addition to hyaluronate, and the same is true of most ground substance. Hyaluronic acid lends to the ground substance certain of its important physicochemical properties, e.g. its viscosity, gelatinous character and water-binding capacity.

The fibril system comprises collagen, reticulin and elastic fibers. The electron microscopic structure and the chemical composition of collagen and reticulin fibers are very similar, whereas those of elastin appear to differ considerably.

All regeneration and repair of connective tissue is initiated by the formation of ground substance. The first step seems to be mucinous organization of an edema fluid. Hyaluronic acid is the dominating polysaccharide in the repair of fibrillar connective tissue during the first few days. Thereafter the content of chondroitin sulfate increases. The mucopolysaccharides stimulate the deposition of fibrils, and thus fibrous organization follows.

The very first steps of regeneration appear to be the most sensitive to hormonal influence. Hyaluronic acid has a rapid turnover. Its biologic half-life is about two days, whereas that of chondroitin sulfuric acid is considerably longer. Once deposited, collagen is a metabolically inert substance.

HORMONES

Hypophysis. As a link or mediator between psyche and soma, the pituitary gland, which is under constant cerebral stimulation, produces a variety of master hormones. These hormones act in part by way of peripheral endocrine glands and their subordinate hormones, in part directly on the tissues.

Corticotropin is a master hormone which stimulates the adrenal cortex to release of its own hormones. Thyrotropin acts upon the thyroid, and directly on connective tissues as well. Somatotropin exerts its action on the tissues. Gonadotropin stimulates hormone production by the gonads, and only by way of these influences mesenchymal tissue.

Cortisol, Cortisone, Corticotropin. Most experimental results have been obtained with cortisone (11-dehydro-17-hydroxycorticosterone) and cortisol (17-hydroxycorticosterone, hydrocortisone). The last-mentioned steroid is the main glucocorticoid formed in the adrenal cortex under the stimulation of corticotropin. The effects of these two adrenal steroids are practically identical. They influence numerous enzyme systems controlling the intermediary protein, lipid and carbohydrate metabolism, and exert an effect on the electrolyte and water metabolism.

The clinical treatment of systemic mesenchymoses has, in effect, constituted an enormous experiment yielding important information concerning the influence of cortisone and cortisol on connective tissue. This effect has been tested on various animals, in morphological as well as chemical studies in laboratories all over the world.

Changes in the structure and functions of connective tissue cells may be visualized in the electron microscope, even in the light microscope. The material studied has included fixed tissue, intact tissue of living animals, and tissue cultures.

The tissue mast cells are sensitive objects responding readily to the administration of cortisone and cortisol. The volume of the cells diminishes, their outlines become irregular and bizarre, and the cytoplasm becomes vacuolated. The granules, which normally fill up the cell body like globular droplets, clump together, forming irregular aggregates. The affinity for certain dyes changes. Normally, the granules stain metachromatically with various basic dyes, e.g. toluidine blue. After being submitted to the influence of the steroids they may take an orthochromatic stain. Unlike normal mast cell granules, those of affected cells vary in size. The number of identifiable mast cells in the tissues is reduced [*1–11*]. These changes must be assumed to be the morphologic manifestation of marked impairment of the function of the cell.

In tissue cultures of embryonic skin and spleen, cortisone (as the free alcohol) has been found to inhibit mast cell activity [*12*].

By autoradiography it has been shown that cortisone inhibits the uptake of ^{35}S-labeled sulfate into the sulfomucopolysaccharides of the mast cells in the connective tissue of skin papillomas in mice [*13*]. This phenomenon was associated with inhibition of carcinogenesis of the skin after painting the skin with the carcinogenic hydrocarbon 9,10-dimethyl-1,2-benzanthracene [*14*]. Applied locally, cortisol acetate

provokes structural changes in the mast cells of induced precancerous papillomas like those mentioned [*15*], parallel with a significant regression of the tumors [*16*]. Similar morphologic changes have been observed in keloids and other fibroses yielding to local treatment with cortisol acetate [*17–20*].

Treatment with cortisone brings about a reduction in the content of histamine in connective tissue of dogs after depletion by tween 20 [*21*]. Using ^{14}C-histidine Schayer et al. [*22*] showed that cortisone inhibits the binding of new histamine to rat skin.

There is some disagreement in the findings concerning the influence of cortisol and cortisone on fibroblasts *in vitro*. Several investigators have demonstrated inhibition of the growth and migration of fibroblasts in cultures [*23–26*]. Others could not confirm the inhibition on the fibroblastic activity. However, cytoplasmic vacuoles were observed at an early stage of outgrowth [*12,27–29*]. The mitotic index has been found to be unchanged [*27,30*].

Cortisol and cortisone are reported to inhibit fibroblastic production of collagen [*31,32*]. In skin wounds of rabbits the content of fibroblasts is reduced if cortisone is applied in doses high enough to inhibit the repair process [*33*].

In inflammation, the migration of polymorphonuclear granulocytes and macrophages may be inhibited by cortisone [*34,35*]. Reticuloendothelial cells are restricted in their regeneration [*36*], and in their enzymic activity against bacteria.

The number of plasma cells in organs of hyperimmunized animals is decreased in response to cortisone influence; this reduction parallels a depression of the globulin concentration in blood plasma [*37*].

In blood as well as in tissues a temporary fall in the lymphocyte count has been observed in cortisone-treated organisms [*38*]. The number of circulating eosinophil [*39,40*] and basophil [*41–43*] granulocytes is consistently decreased. Similar results have been obtained with corticotropin [*41,42*]. The decrease in the eosinophil count may be due to a migration from blood to tissues [*44*].

The intercellular substance is changed and reduced in amount [*1,2,45,46*]. The content of acid mucopolysaccharide is lowered. The amount of hexosamine, an essential component of mucopolysaccharides, decreases [*47,48*]. In normal and diseased synovial fluid, cortisone has been shown to invoke an increase in the polymerization of hyaluronic acid [*49–51*]. After removal, the newly formed synovial fluid in rheumatic joints shows increased viscosity, but its amount is reduced under the influence of cortisol and cortisone, and there is no increase in hexosamine concentration [*49*]. Cortisone inhibits the synthesis of chondroitin sulfuric acid in regenerating connective tissue [*52,53*]. In the skin and in the sclera and cornea of the eyes of guinea pigs, the incorporation of ^{35}S-labeled sulfate is reduced [*54*]. Various adrenal steroids inhibit the incorporation of ^{35}S in cartilage slices [*55*].

By changing the connective tissue ground substance, cortisone increases the spread of injected indicators in the skin of rabbits and human subjects, whereas the spreading capacity of hyaluronidase is inhibited, apparently because of alteration of hyaluronate by cortisone [*56*]. Corticotropin has a similar effect in living animals [*57,58*]. Adrenalectomy brings about an increase in the spreading effect of testicular hyaluronidase [*59,60*]. In the skin of dead animals, hyaluronidase spread is not inhibited, however; thus reduction of capillary permeability may play an important role [*61*].

Following local application of cortisone acetate to rat skin there is a reduction in the relative amount of ground substance, the collagen fibril bundles being arranged in a denser mass and the skin being thinner than normal [*46*]. During treatment of myxedematous patients with corticotropin a regression of the mucin accumulation has been observed [*62*]. The uptake of ^{131}I was not increased. The effect was interpreted as an action upon the connective tissue like that already described, not a result of possible contamination with thyrotropin.

Mineralocorticoids. Few experiments are available to show the influence of aldosterone and cortexone (desoxycorticosterone) on mesenchymal tissues. The general opinion is, however, that their effects are entirely different from and in some respects counteract those of cortisone and cortisol [*63*]. Aldosterone stimulates the formation of foreign body granuloma [*64*]. Cortexone acetate (DOCA) stimulates the proliferation and activity of fibroblasts in connective tissue repair [*65*], as well as the formation of granulation tissue around turpentine abscesses [*66*]. In tissue cultures, however, fibroblastic growth seems to be inhibited by cortexone [*24*].

Thyrotropin. It is a well established fact that, besides stimulating the thyroid gland, the

thyrotropic hormone produced by the anterior pituitary gland exerts a direct effect on the connective tissues [*67,68*]. In thyroidectomized guinea pigs, systemic administration of a thyrotropic anterior pituitary extract causes mobilization of fat from the normal depots, with subsequent hyperlipemia and deposition of fat in the liver, the skeletal and cardiac muscles, and the renal tubules. During the time of this transport the blood leukocytes phagocytize droplets of fat. In the tissues the fat is replaced by a mucinous substance with a considerable content of acid mucopolysaccharides, in certain phases of progression primarily hyaluronic acid [*67,69*]. If the thyrotropin stimulation continues, exophthalmos appears. These phenomena may be observed even in partially or non-thyroidectomized animals, but in such subjects the increased release of thyroid hormone from the thyroid gland soon inhibits the action of thyrotropin. Exogenous d,l-thyroxine in doses rendering guinea pigs thyrotoxic prevents the fat-mobilizing, mucotropic and exophthalmogenic action of thyrotropin [*69,70*].

It has been possible to separate a thyroid-stimulating principle from an ophthalmotropic principle [*71–73*]. There is much evidence that the fat-mobilizing, mucotropic and ophthalmotropic effects are caused by one hormonal principle which is closely linked to the thyroid-stimulating factor [*67,74*].

In many respects the effect of thyrotropin on connective tissue is the reverse of that of the glucocorticoid hormones. In response to thyrotropin the mucinous system of the connective tissue is stimulated. The mast cells appear voluminous, and their cytoplasm is loaded with mucopolysaccharide-containing granules [*67,75, 76*]. In living animals, release of this substance from the cells to the intercellular compartment may be observed under the microscope. It is metachromatic and sensitive to testicular and bacterial hyaluronidase [*75*]. This characterizes hyaluronic acid. An increase in the water content of the intercellular substance may act as a stimulus for release of mucopolysaccharides from the ground substance. The water-binding capacity of hyaluronic acid being exceedingly great, the result is a mucinous edema [*77,78*]. These phenomena appear to be taking place all the time in the normal organism, and they may be fundamental factors in the function of the connective tissue as a water depot.

In organisms overstimulated with thyrotropic hormone, e.g. after thyroidectomy or in diseases of the thyroid gland, the intercellular amount of acid mucopolysaccharide, including hyaluronic acid, is considerably increased [*79,80*]. A release of this material elicited by extracellular edema which may be produced, e.g. by increased capillary permeability, results in mucin accumulation in the extracellular space [*81*]. This hydrated gel is the substance which has given rise to the term myxedema. The hormonal action manifests itself in all parts of the body, e.g. in the perirenal, axillary and peritesticular regions, but most distinctly in the retrobulbar tissue [*67*]. It is generally agreed that vascular lesions and nervous regulation of the vascular tone may play an important part in the development of tissue changes of this nature and that they account for the unequal distribution of the mucinous substances in various dyscrine states.

The changes in the retrobulbar tissues in thyrotropin-induced exophthalmos [*82,83*] are of the type mentioned, viz. accumulation of mast cells, primarily around the vessels, and of extracellular acid mucopolysaccharides, especially hyaluronic acid [*67*]. These changes are found in the connective tissue around as well as in the extraocular muscles, the Harderian and the ventral lacrimal glands. The hexosamine content of the retrobulbar tissues is significantly increased, indicating an increased concentration of mucopolysaccharide, and so is their content of water [*84*]. The accumulation of hyaluronic acid is sufficient explanation of the bulbar protrusion [*67*].

A pepsin-digested thyrotropin preparation with ophthalmotropic activity has been shown to increase the uptake of ^{35}S-labeled sulfate by the Harderian and the ventral lacrimal glands in guinea pigs. The uptake parallels the doses of hormone and may be used as an assay method for the ophthalmotropic activity of pituitary extracts [*85*]. Thyroidectomy and administration of thyrotropin are followed by an increase in the viscosity and the glucosamine content of the vitreous body of rabbits [*86,87*]. In guinea pigs an increased uptake of ^{35}S has been observed in skin, cornea and sclera [*54*] as well as in retrobulbar tissue [*88*].

In the inner ear, thyrotropin stimulates the mucinous system. In the labyrinth of thyroidectomized guinea pigs there is an increase in the number and size of mast cells. The hexosamine concentration of the endo- and perilymph does not change, but there seems to be an influx of

water. In the experiments reported so far, disturbances of the vestibular functions have been observed [*89*].

The increased hyaluronic acid content of the connective tissue ground substance of thyrotropin-stimulated and myxedematous subjects explains the decreased spread in their skin and the increase in the spreading effect of hyaluronidase. In such persons the enzyme finds a suitable substrate on which to act [*45,79*].

Collagen formation seems not to be stimulated to any great degree by thyrotropin in the absence of simultaneous somatotropin activity.

Thyroid. The thyroid hormone acts as an inhibitor of thyrotropin release from the hypophysis, and prevents the typical thyrotropin effects in animal experiments [*69*]. Contrary to the action of thyroxine, dinitroorthocresol [*90*] or sulfuric oil [*69*] administered to guinea pigs increases the metabolic rate without affecting thyrotropin-induced changes in connective tissue. The activity of the mucinous system is restricted by thyroxine; the mast cells appear small and their granules are few [*75,76*]. During treatment of myxedematous patients with thyroxine the blood count of basophil leukocytes decreases [*91*]. The content of acid mucopolysaccharides, sulfated as well as non-sulfated, in the ground substance decreases [*79,87,92*]. Thyroxine increases the spreading of fluids in skin and subcutaneous tissue [*79,93*]. The hexosamine concentration in the retrobulbar tissue and in the vitreous body [*87,94*] of guinea pigs decreases, and so does the concentration of hyaluronic acid in articular tissue [*95*] and the water-binding capacity of the skin [*50*].

Thyroxine has been shown to reduce the incorporation of ^{35}S-labeled sulfate into sulfomucopolysaccharides in growing connective tissue, and possibly through this action inhibits the formation of collagen fibers [*92*].

Somatotropin. In some respects the effect of the growth hormone on connective tissue is similar to that of thyrotropin. It is not quite clear which effects are due to thyrotropin contamination of the extracts used; but the effects already summarized in this report have been obtained with thyrotropic pituitary extracts almost completely freed of growth hormone.

In several experiments somatotropin administration brought about stimulation of the functions of the mast cells, including mucopolysaccharide formation [*75*], as well as a stimulation of fibroblast proliferation in granulation tissue [*96*] and of collagen production by the fibroblasts [*97*]. Reticuloendothelial cells have also been reported to increase. By these effects somatotropin may induce changes suggesting arthritis in rats [*98*].

Parathyroid Hormone. This hormone seems to affect the collagen at various sites. A dissolution of bone matrix and an increase in urinary mucoprotein output has been observed [*99*]. Various authors have stated that the permeability of the connective tissue of skin decreases in response to parathyroid hormone. Others have not been able to confirm these observations.

Sex Hormones. It is important to realize that there are important differences in the effect of sex hormones on connective tissue from species to species, as well as between the two sexes. It is generally agreed that the connective tissue effects of the sex hormones control and determine the secondary sex characters of mammals. Even normal fertility may depend on the hormonal influence upon mesenchymal fluids and tissues.

Estrogenic Hormone. In several animals estrone induces an increase in the content of acid mucopolysaccharide, particularly hyaluronic acid, in all connective tissues [*100–102*]. Spreading of fluids in the skin of rabbits and other animals is restricted, and so is the permeability of the small blood vessels [*102–104*]. In the sex skin of young macaque monkeys the production of hyaluronic acid is stimulated, an observation which has been confirmed in oophorectomized monkeys [*105,106*].

The incorporation of radiosulfate (^{35}S) in the mucous membranes of the uterus, Fallopian tubes and vaginal wall is stimulated by estrogens, and so is the activity of the tissue mast cells [*107*].

Progesterone seems to counteract the tissue effect of estrone [*108*].

Relaxin influences the pelvic connective tissue during pregnancy. The tissue content of water increases, and the mucin content along with it [*109–111*].

Testosterone. During growth of the cock's comb, which is governed by testosterone activity, an accumulation of hyaluronic acid takes place [*112*]. Only traces of chondroitin sulfate have been demonstrated [*113*]. α-estradiol inhibits normal but not testosterone- or gonadotropin-stimulated growth of the comb in chickens [*114*]. Cortisone also inhibits the formation of mucopolysaccharide in the comb [*115*]. Testosterone has been shown to increase collagen formation in the skin of capons [*116*].

Gonadotropin. Gonadotropic pituitary extracts stimulate the production of hormones arising from the gonads and act exclusively by way of these. Ten to fifteen hours after injection of gonadotropin to rabbits, and after coitus or other sexual excitement, a drop in the count of blood basophils has been observed [*117*]. After ovulation an accumulation of basophil leukocytes has been found around the ovulated follicles and in the vessels of the ovaries, oviduct and uterus. Thus a migration from blood to tissues seems to take place in response to certain physiological requirements [*118*].

REGENERATION AND REPAIR

Wound and Fracture Healing. Adrenal steroids: The healing of surgical wounds and the development of granulation tissue is inhibited by cortisol, cortisone and corticotropin in human subjects as well as in experimental animals [*33,119*]. The formation of ground substance and collagen fibrils and the ingrowth of vessels is restricted. During cortisone treatment of rats the oxygen uptake by wound tissue is reduced [*120*] and so is the tensile strength of sutured experimental wounds, the degree depending on the dosage [*121*]. It is generally agreed that the healing of wounds depends on the species and on several factors beside hormonal control, e.g. the nutritional state of the animal, and the vitamin and protein supply. The cells in the wound and the ground substance are targets of the hormonal effect [*122*]. In man, inhibition of wound healing rarely takes place after administration of steroids in therapeutic doses. In rabbits, the formation of granulation tissue may be delayed for a few weeks; thereafter the granulations develop unrestricted [*123*]. In some animals skin homografts may be tolerated by cortisone-treated hosts [*124,125*].

In animals, fracture healing is also retarded, the absorption of blood, callus formation and the regeneration of collagen being inhibited and delayed [*126*].

Thyroxine: Moltke [*92,127–130*] observed that L-thyroxine reduced the tensile strength of healing wounds in normal as well as thyroidectomized guinea pigs. On the other hand, the tensile strength was increased somewhat by D-thyroxine. This isomer only moderately increases the metabolic rate of the tissues, but inhibits pituitary release of thyrotropin. Thyroxine inhibits the uptake of ^{35}S sulfate by wound tissue. D,L-thyroxine did not influence the low tensile strength of incised wounds in scorbutic guinea pigs. Injection of ascorbic acid raised the level but did not change the nature of the dose-response curve of thyroxine. Moltke concluded that D,L-thyroxine inhibits the formation of collagen fibrils, and that the target is located in the wound tissue. Upon administration of thyroxine together with a dehalogenase inhibitor, wound healing was restricted and retarded even more than during treatment with thyroxine alone, presumably because thyroxine was not deiodinated and inactivated [*13*]. Thyrotropic hormone did not significantly influence the tensile strength of the wounds.

Somatotropin: The tensile strength of experimental wounds is increased after local treatment with growth hormone [*132*]. In other experiments, however, it did not stimulate growth of tissues in wounds already inhibited by cortisone [*133*]. Low doses of the hormone seem to be optimal, whereas high doses may result in inhibition [*134*].

Sex hormones: Testosterone and estradiol stimulate the formation of granulation tissue in inflammatory processes if somatotropin is present [*96*].

Serosal Adhesions. Physical and chemical injury to the peritoneum or pleura may elicit connective tissue adhesions, the development of which follows a pattern similar to that of the healing of wounds. Systemic administration of cortisone or corticotropin inhibits the development of serosal adhesions [*135,136*]. Intraperitoneal deposition of cortisol acetate prevents the fibrous organization of the mucin and fibrin formed in response to sprinkling of the intestine with talc, surgical injury to the serosa, separation of fully developed adhesions, and intestinal anastomosis [*18,137–139*].

TUMORS

The connective tissue stroma plays an important role in the integrity, development, growth and spreading of various tumors. By influencing the connective tissue, cortisone and cortisol have been shown to influence epidermic tumors induced by painting of the skin of mice with carcinogenic hydrocarbons. Systemic administration of cortisone inhibits the development and prolongs the latent period of skin papillomas induced by a single painting with 9,10-dimethyl-1,2-benzanthracene [*14,140,141*] or benzpyrene [*142*], but repeated paintings with methylcholanthrene for six weeks have been followed by an increase in the tumor incidence [*143*].

Fully developed skin papillomas regress in response to local injections of cortisol acetate into their stroma [*16*]. During the first weeks, carcinomas induced by repeated paintings with 9,10-dimethyl-1,2-benzanthracene have shown a similar response, but after eight to eleven weeks they resumed their growth despite continued weekly treatment [*144*]. Cortisol produced marked morphologic changes in the tumor connective tissue. The mast cells changed, and their production of mucopolysaccharide was inhibited. This may be of some importance as mast cells abound in the stroma of precancerous papillomas as well as in many other tumor types, including human neoplasms [*15,145–147*]. When skin papillomas become malignant, the mast cell count is reduced [*146*]. There is still insufficient support of the theory that mast cells and their extracellular products form a barrier against spread of tumors [*146*].

Cortisone treatment of the host animal facilitates heterologous transplantation of tumors [*148*], partly by way of its connective tissue effect.

In thyroidectomized mice, thyroxine decreases the number of tumor-takes after one painting of the skin with 9,10-dimethyl-1,2-benzanthracene [*149,150*]. Thyroidectomy, on the other hand, increases the number of tumors [*150*].

Somatotropin. In some experiments the growth hormone has been reported to stimulate, in others not to influence the growth of various tumors [*151–153*], and to counteract the inhibitory effect of cortisol [*154*]. There is no experimental evidence to indicate, however, whether these effects are mediated by way of connective tissue changes.

Sex hormones are also known to influence various tumors of different types, but the role of the connective tissue as the target organ is not sufficiently elucidated.

INFECTION

When hyaluronidase-producing bacteria invade connective tissue they break down the hyaluronate of the ground substance, changing the substrate from a viscous to a watery material. The bacteria as well as their toxins are thus allowed to spread. At the very moment of breakdown of ground substance mucopolysaccharides, some of the degradation products counteract the enzyme, reducing the permeability of the connective tissue. However, others seem to promote it [*56,155–157*]. This process is influenced by hormones.

Cortisone inhibits the new formation of hyaluronic acid. Long-term treatment with cortisone or similar steroids reduces the resistance to infection. Low doses, however, may have a protective effect [*158*]. Cortisone does not influence the microorganisms directly [*159*].

Growth hormone stimulates the formation of granulation tissue in response to infection [*96, 156,160*]. Estrogenic hormones inhibit the spread in the skin of rabbits and mice [*104*]. It is a well known fact that in young women the resistance to invasive bacteria may be lowered during the premenstrual period. This may be due to an increase in hyaluronic acid in the connective tissue, accounting for the increased binding of water, among other things.

INFLAMMATION

The reaction of connective tissue to injury is influenced by hormones which control regeneration and capillary permeability. Any change in the condition of the connective tissue alters the inflammatory process and the balance between the noxious agent and the host.

Adrenal Steroids. By an action on the cellular origin of histamine, cortisone inhibits vascular permeability and exudation [*161*]. Fibrin formation is restricted, too, and so is the concourse and phagocytic activity of leukocytes and reticuloendothelial cells [*34,35*]. The blood flow through inflamed areas is reduced by cortisone and cortisol [*162,163*], and the formation of granulation tissue is inhibited [*63,122,123*]. Glucocorticoids evidently do not influence the first steps of inflammation, but after twenty-four hours the inhibition of exudation and fibrin formation is obvious [*164,165*].

Thyroid hormone inhibits the inflammatory reactions of connective tissue, whereas thyrotropin and particularly somatotropin stimulate them [*96,127,156,160*].

Sex hormones. Estrogenic hormones establish a further barrier to the spread of tubercle bacilli and other infections [*103*] in rabbit connective tissue.

FERTILITY

The growth of the Graafian follicle is controlled by estrone and progesterone. The production of the cavity, the water content and the growth of the follicular sac are results of changes in acid mucopolysaccharides. In small follicles the concentration of hyaluronic acid is high, whereas in the less viscous fluid of the larger

follicles chondroitin sulfate is the predominating mucopolysaccharide. After stimulation by coitus or injected gonadotropin, the ovarian follicles of rabbits do not incorporate ^{35}S-sulfate in the follicular fluid [*166*]. In mature follicles depolymerisation of the hyaluronic acid takes place, probably by hyaluronidase activity; as a result, the osmotic pressure increases, leading eventually to rupture [*167,168*].

Fertilization, i.e. fusion of the spermatozoon with the ovum, takes place only if the hyaluronidase-containing sperm is able to break down the hyaluronate of the mucinous mass surrounding the egg after release from the ovary. The production of hyaluronate in the ovarian follicle is subject to hormonal control.

It is well known that young women retain water in their tissues before and during the early menstrual period and in advanced pregnancy. As a result, they exhibit weight gain and decreased urinary output. The absorption of a solution of uranin from the skin is accelerated [*169*], and diffusion of intracutaneously injected saline solution takes place more rapidly in the premenstrual period [*170*]. These changes are probably provoked by estrogenic hormone.

During late pregnancy a certain relaxation of the symphysis and other pelvic connective tissues take place. The tissues become softer, succulent and can be stretched [*110*]. The hormone relaxin may be responsible for these changes.

ENDOCRINE DISEASES

Hypophysis. Acromegaly and gigantism involve increased activity of growth hormone and thyrotropin. Growth and regeneration of connective tissues are stimulated. The tissues are ample and fibrous, the skin thickened and coarse, and fibromas and keloids are common. Similar hypertrophy and proliferation are present in bones, cartilage and vessel walls. The arteries may be considerably enlarged and their walls thickened. Stimulation of the production of intercellular material is noted throughout the connective tissues. The bundles of collagen fibrils are thick and the papillae corii are large and plump [*171,172*]. An increase in the reticuloendothelial cell count also has been observed.

Hypophysis—Adrenal Cortex. The most evident symptoms of hypercorticism in Cushing's syndrome are due to the effects of cortisol on connective tissues. Fatty tissue accumulates, partly at the cost of mucin, and the connective tissue is reduced. The skin is thin, so that the vessels become more readily visible. Dermal striae on the abdomen, hips and shoulders indicate degeneration of the collagen and elastic tissue, with reduction of tensile strength and elasticity. A similar action on the vascular connective tissue entails dilatation and fragility leading to rupture and hemorrhages upon minor injury. These changes may result in cerebral hemorrhage, particularly in cases of co-existing hypertension. Cutaneous purpura and ecchymoses are well known phenomena. Muscular weakness is an outstanding feature. The collagen and ground substance of the bones are affected. There is depletion of calcium, phosphorus and nitrogen; spontaneous fractures and collapse of vertebrae may result. During excretion of the mobilized calcium, calculi may form in the urinary tract. Healing of fractures and wounds as well as repair and regeneration of all connective tissue are retarded and impaired. The hypertrichosis and hirsutism of patients suffering from Cushing's disease may be due to a dyshormonal action on the mesenchymal root sheaths of the hairs. Lowered resistance to infections has some bearing on the influence of adrenocortical hormones on connective tissue ground substance. Parallel with this effect there is a depression of the cellular and humoral defense, antibody formation by reticuloendothelial cells and phagocytosis being inhibited. Blood eosinopenia, basopenia and lymphopenia also are signs of hypercorticism.

Similar symptoms are well known side effects of corticotropin, cortisone, cortisol or related steroids in the treatment of connective tissue disorders.

Hypophysis—Thyroid. In hypothyroidism there is an increased amount of ground substance in most connective tissue, including the skin. The content of hyaluronate and chondroitin sulfate is more or less increased, and the mucinous edema may be evident upon gross examination of the skin, thus presenting a true myxedema. The mucopolysaccharide accumulation is considerable in the corium, particularly in the papillary layer. During active phases the subcutaneous fat is gradually mobilized and replaced by mucin. Large mast cells accumulate in the perivascular areas as well as free in the connective tissue. The collagen fibril bundles are split apart by the mucinous edema; often they show considerable degeneration, being swollen and basophilic [*173,174*]. Spreading of injected fluids is inhibited, but hyaluronidase has marked spreading power in myxedematous skin because its substrate,

hyaluronic acid, is ample and usually highly polymerized [*79*]. The increased mast cell activity, involving mucopolysaccharide formation, and fat mobilization occur not only in the skin and subcutis but also in the interstitial connective tissue of cardiac and skeletal muscles [*171*], in the joints, and in other sites as well. Mucinous edema in the articular connective tissue and an increased concentration of hyaluronic acid in the synovial fluid may be of some pathogenic importance in relation to the joint symptoms which accompany some cases of myxedema [*175*]. There may be moderate swelling and limited mobility but true inflammation is always slight and the condition never causes permanent damage.

Myxedema is often accompanied by infertility. The "myxedema heart," the constipation, loss of hair, hoarseness, impaired acoustic and vestibular functions, and mental disorders may all be due to altered distribution of mucin in the connective tissue. There is some evidence to suggest a relationship between Ménière's disease and dysfunction of the thyroid gland [*176*]. The reported findings of Poulsen [*89*] support this assertion.

The changes in myxedema described correspond to the picture of thyrotropin stimulation in animal experiments. They occur in patients with impaired thyroid function and in thyroidectomized subjects. In such persons inhibition of the pituitary release of thyrotropin is reduced or absent.

In addition to myxedema, thyrotropin stimulation plays a pathogenic role in thyrotoxicosis, malignant exophthalmos, circumscribed myxedema and acromegaly. In hypothyroidism the effect of the fat-mobilizing and mucotropic principle is immediately recognized. Malignant exophthalmos represents primarily the effect of the ophthalmotropic factor, whereas in thyrotoxicosis thyroid stimulation is the feature which determines the clinical picture.

Malignant exophthalmos, often accompanied by circumscribed pretibial myxedema, is a pituitary syndrome which may arise after thyroidectomy, ^{131}I-treatment of thyrotoxicosis, or other sudden removal of marked inhibition by the thyroid. The retrobulbar changes are comparable to the histological changes found in thyrotropin-induced exophthalmos in guinea pigs [*82,83*]. There is edema of the connective tissue, including that of the extraocular muscles, which may attain a volume several times larger than that of normal muscles. The number of mast cells and thus also the accumulation of acid mucopolysaccharides is increased.

Circumscribed myxedema may be present in euthyroid, hyper- or hypothyroid patients. A prominent feature is mucin and mast cell accumulation of a type similar to that described in myxedema, only more pronounced [*45,172*]. There is some evidence that increased capillary permeability due to preceding thyrotoxic damage of the vessel walls, and thyrotropin-induced stimulation of mast cell activity are both factors of pathogenic importance [*81*].

In patients with an elevated level of thyrotropic hormone in the blood serum, i.e. in the groups of myxedema, thyrotoxicosis, malignant exophthalmos and acromegaly, a characteristic change in the cardiac and skeletal muscles, including the extraocular muscles, has been observed [*74,83,177*]. A substance containing acid mucopolysaccharide of the hyaluronic acid type accumulates beneath the sarcolemma. Having an unusually marked water-binding capacity, this substance may account for the edema and increase in the volume of the extraocular muscles as well as for the reduction in muscular strength which characterize these conditions.

In states of hyperfunction of the thyroid gland (thyrotoxicosis), regeneration of connective tissue is impaired. There is a reduction in the ground substance in the dermis as well as in other mesenchymal tissues. The mast cells are small, faintly granulated and scarcely demonstrable except around the smaller vessels. Spreading in the dermis and the subcutis is increased [*79,93*]. The skin is thin and soft, warm and moist, hyperemic, showing vascular lability.

Hypophysis—Gonads. Apart from influencing the secondary sex characters, hypogonadism does not involve characteristic changes in the connective tissues in man.

HORMONE THERAPY

In conditions of hormonal insufficiency, substitution therapy obviously is indicated but even in diseases which cannot be ascribed to an endocrine disorder, hormone preparations are used for the purpose of influencing injurious tissue changes. Systemic connective tissue diseases, especially in their phases of progression, may respond readily to treatment with corticotropin and adrenocortical steroids of the glucocorticoid type. In cases in which changes in the mucinous system of the connective tissue predominate, the

beneficial effect may be reflected within hours or days. During this period the physicochemical state of the entire connective tissue system may be profoundly altered. This is true, e.g. of rheumatoid arthritis, iridocyclitis and glaucoma, dermatomyositis, urticaria, and disseminated lupus erythematosus. In the more complicated mesenchymoses in which collagen deposition, among other changes, characterizes the picture, the response may be slight and delayed. Progressive stages of scleroderma respond to steroid therapy, whereas old "burned out" cases may not respond at all.

Thyroid hormone is used in hypothyroid disease, and its resolving effect on myxedematous connective tissue changes is well known. It is also used, however, in order to influence quite different disorders of connective tissue, e.g. scleroderma and perniosis, although with dubious benefit.

Sex hormones are widely used in the treatment of medical diseases. On the whole it must be emphasized that there is hardly any sphere, apart from hypogonadism, in which their benefits are convincing.

Side effects due to overdosage of hormones are often observed, especially in the long term treatment of mesenchymal diseases with adrenal steroids and in the treatment of myxedema with thyroid hormone. These effects are reflected by primary changes in the connective tissue. Treatment with hormones may involve balancing between the intended beneficial effects, which are to normalize pathological processes and changes, and untoward effects which entail changes even in unaffected tissues.

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Clinicopathologic Conference

Multiple Myeloma with Renal Failure

STENOGRAPHIC reports, edited by Lillian Recant, M.D. and W. Stanley Hartroft, M.D. of weekly clinicopathologic conferences held in the Barnes and Wohl Hospitals, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine, Preventive Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

A FIFTY-NINE year old white man was admitted to the Barnes Hospital on September 11, 1957 with complaints of inability to walk, nausea, and back pain. He died on September 21, 1957.

The history as given by the patient was somewhat confused. He had been in good health until about seven years previously when he was found to have hypertension. Six years before admission he began to have transient black-out spells which were usually associated with standing up rapidly. Following one of these episodes, a diagnosis of "heart attack" was made and the patient was treated for the condition at home without bedrest. He was subsequently given a low salt diet and one "heart pill" a day which he continued to take for one to two years. Three years before admission he had noted marked edema of the ankles without swelling of the face or abdomen. The edema had subsided about one year before admission. For several years he had complained of aching in the back without other bone or joint pain. In addition he had had frequent episodes of substernal and epigastric aching and burning. These symptoms were worse after meals and were associated with occasional vomiting. There was no food intolerance, or hematemesis, or tarry stools. Three months before admission the patient had had frequency, urgency, chilly sensations and bilateral flank pain lasting about one week. At this time he passed cloudy urine. In July 1957 he fell, striking the left side of his chest. Because of subsequent symptoms of aching in his chest, roentgenograms were obtained; these revealed a fractured thoracic vertebra. Because of generalized abdominal and back pain, and weakness, he became bedfast during August. In the three weeks before admission he vomited one to three times a day and noted intermittent mild fever, night sweats, nocturia, and back pain radiating into the groin. He had lost 30 pounds of weight since June.

Past history revealed that the patient had had jaundice for two to three months in 1916. An operation for ruptured appendix had been performed in 1930. There was no history of facial edema, smoky urine, or Bright's disease. Chronic renal disease, urinary stone formation, or hematologic diseases had not been recognized in his family.

The patient had worked as a garage mechanic for forty years. He was described as a "non-smoking, non-drinking, God-fearing man" who, to avoid temptations, had never even gone to movies.

Physical examination revealed a blood pressure of 120/80 mm. Hg, pulse 90, respirations 20 and temperature 37°C. The patient was a weak, middle-aged white man who could sit up only with difficulty. A 1.5 cm. area of ecchymosis was present on the right arm. The nail beds were pale and the lunulas were absent. Examination of the fundi revealed narrowed arteries but no hemorrhages or exudates. A 0.5 cm. vesicular lesion with a hemorrhagic border was present in the right buccal mucosa. There were no masses or venous distention in the neck. The chest expanded symmetrically with respiration. The lungs were clear to percussion and auscultation. The lateral border of cardiac dullness could be percussed at the anterior axillary line in the fifth interspace. There was a grade 3, blowing, precordial systolic murmur over the whole precordium, loudest in the second right interspace but not transmitted to the neck. No organs were palpated in the abdomen. There was a suggestion of a pulsatile mass in the epigastrium, and vague generalized abdominal tenderness without rebound. The prostate was not enlarged. Tenderness was present in the area of the

eleventh thoracic vertebra; slight flank tenderness bilaterally was detected by several observers. Reflexes were brisk, active and equal.

The laboratory data were as follows: white blood cell count 9,200 per cu. mm., with a differential of 7 per cent bands, 32 per cent segmented forms, 56 per cent lymphocytes, and 5 per cent monocytes. Repeat examination of the peripheral blood film on September 16, 1957 showed 2 per cent eosinophils, 2 per cent band forms, 70 per cent segmented forms, 20 per cent lymphocytes, and 6 per cent monocytes. The packed red blood cell volume was 23 per cent. Examination of the urine disclosed a specific gravity of 1.008 pH of 4.5, and 4-plus proteinuria. The result of the test for Bence Jones protein was positive and of the Sulkowitch test for urinary calcium 2 to 3 plus. There were many calcium oxalate crystals. In addition, 10 to 20 white blood cells per high power field were seen in the urine sediment. The blood non-protein nitrogen was 137 mg. per cent, sodium 135 mEq. per L., potassium 5.5 mEq. per L., chloride 104 mEq. per L., and CO_2 17 mEq. per L. Urine electrolytes in a twenty-four hour volume of 1,800 ml. revealed a sodium concentration of 36 mEq. per L., potassium 22 mEq. per L., and chloride 35 mEq. per L. The urine protein concentration was 4 gm. per L. in the same specimen. The serum albumin was 5.5 gm. per cent and the globulin 1.8 gm. per cent. Blood calcium was 13.4, phosphorus 8.1 and the uric acid 7.5 mg. per cent. The alkaline phosphatase was 2.9 Bodansky units. The electrocardiogram was within normal limits. Roentgenologic examination of the chest was interpreted as showing left ventricular enlargement and healing fractures of the right and left tenth ribs. Skeletal films revealed generalized osteoporosis, mild compression fractures of the eleventh and twelfth thoracic and the first lumbar vertebrae, and multiple well defined areas of radiolucency throughout both femurs and the skull. These findings were considered compatible with the diagnosis of multiple myeloma. Partially calcified arteries were described in the area of the right wrist and between the shafts of the first and second metatarsals in the feet. There was a questionable area of radiolucency at the base of the first phalanx of the second right toe. Multiple gallstones were seen in the upper right quadrant of the abdomen. The renal shadows were thought to be normal in size, and calcification in the area of the kidney was not detected. Results of tests for macroglobulinemia (Sia test) and cryoglobulinemia were negative. The corrected sedimentation rate was 10 mm. per hour, uncorrected 46 mm. per hour (Wintrobe). In the samples of aspirated bone marrow, some areas showed almost completely normal marrow with adequate erythropoiesis and only scattered plasma cells; in other areas, there were solid sheets of abnormal plasma cells. Some of the plasma cells were undergoing mitosis, others were binucleated. Erythropoiesis seemed to be depressed with 9 normoblasts per 100 white blood cells. The marrow differential was recorded as 82 per cent abnormal plasma cells, with 4 per cent segmented forms, 2 per cent bands, 2 per cent myelocytes, 1 per cent eosinophils, and 7 per cent lymphocytes. A culture of a clean voided specimen of urine was described as containing a moderate growth of staphylococci, diphtheroids, and non-hemolytic streptococci, but a repeat culture was negative. The clotting time was six minutes. Serum electropheresis was unofficially described as normal.

During the patient's hospital stay he was afebrile most of the time with maximal temperatures of 37.8°C. on September 11 and 13. Urine output was approximately 1 L. per day except on September 20 when a urine volume of 500 ml. was recorded. He was treated with a low protein, high fat, high carbohydrate diet, and tetracycline, 250 mg. administered every six hours. On September 13, the blood non-protein nitrogen was 158 mg. per cent, serum sodium 134 mEq. per L., potassium 5.2 mEq. per L., chloride 107 mEq. per L., and CO_2 15.8 mEq. per L. Beginning on September 14, his course was complicated by repeated episodes of vomiting in amounts varying from 250 to 1,050 ml. per day. Serum electrolyte determinations on September 16 were essentially unchanged. Because of the persistent vomiting, tetracycline was given parenterally and chlorpromazine (25 mg.) was injected four times a day intramuscularly. The patient also required frequent injections of meperidine for pain. He was treated with urethane on September 18 and received a total of 6.5 gm. over the next four days. On September 20 the blood non-protein nitrogen was 185 mEq. per L. and the patient was noted to be hypotensive. From that time until death, he required intermittent doses of Vasoxyl® (intramuscularly) to maintain a systolic blood pressure of 90 to 100 mm./Hg. He was given a transfusion of 500 ml. of packed red cells. On September 21, the

patient died immediately following a generalized seizure lasting thirty seconds.

CLINICAL DISCUSSION

DR. EDWARD REINHARD: Dr. Humphrey, will you discuss the roentgenograms?

DR. HARVEY HUMPHREY: I have selected the films that demonstrate discrete localized zones of osteolysis. The diagnosis was compatible with multiple myeloma. Rather discrete lesions were seen in the femora bilaterally. They were not symmetrical. The destruction involved the cancellous bone as well as the adjacent cortex. The bones were somewhat demineralized. Femoral arteries showed a rather striking degree of sclerosis, with the characteristic appearance of the Monkeberg type of arteriosclerosis. A film of the spine demonstrated compression fractures of D_{11}, D_{12} and L_1 with compression of the vertebral centrum. All the bones in the spine were demineralized. An incidental finding was the presence of opaque gallstones. Routine chest examination showed the heart to be slightly enlarged with the configuration indicating primarily left ventricular enlargement. Arteriosclerosis of the aorta and a calcified primary complex were also seen. There was a slight deviation of the subglottic region of the trachea, which made us suspicious of enlargement of the superior left parathyroid. We recommended a barium swallow in an attempt to establish that, but the patient was apparently never able to tolerate the examination. There was a localized lesion in the right sixth rib, with a deformity indicating a previous fracture. Most of the ribs appeared abnormal. Abdominal films showed localized zones of increased density in the renal areas due possibly to nephrocalcinosis. The kidneys looked small for a patient of his stature. We have never seen dense kidneys due to the presence of amyloid.

DR. REINHARD: Dr. Moore, these roentgenograms showed two of the classic findings associated with myelomatous involvement of bone. One was the osteolytic lesion with no surrounding bone reaction and the other was generalized osteoporosis. Would you comment on the pathogenesis of the osteoporosis in this disease? Why is it seen in myeloma but not in patients with a marrow infiltrate of similar degree due to leukemia?

DR. CARL V. MOORE: I cannot answer that question, Dr. Reinhard, but one does rarely see severe osteoporosis in acute lymphocytic leukemia as well. I am not aware that decreased osteoblastic activity has been demonstrated in multiple myeloma. In contrast to the ordinary forms of osteoporosis in which the serum calcium is almost always normal, however, the serum calcium is often elevated in myeloma indicating a rather rapid loss of calcium from the skeleton.

DR. REINHARD: Do you have anything to add to that, Dr. Daughaday?

DR. WILLIAM DAUGHADAY: The question of hypercalcemia will probably be up for further discussion. I do not have anything further to add now.

DR. REINHARD: The diagnosis of multiple myeloma was clearly established. Unless there are dissenting voices, we will concentrate on some of the fascinating aspects of the pathologic physiology of this disease, and their relation to the complications experienced by our patient. The protein abnormalities seem to be responsible for many of the difficulties which develop in multiple myeloma. Dr. Mohler, will you summarize the principal protein abnormalities found in plasma and urine?

DR. DANIEL MOHLER: Most patients who have multiple myeloma have some dysproteinemia. In fact if urine as well as serum electrophoresis is performed, 95 per cent show an abnormal protein pattern. The electrophoretic abnormality is characterized by the appearance of a remarkable homogeneous protein which forms a very definite and narrow peak in contrast to the broad band found in patients who have hyperglobulinemia for other reasons. Approximately 85 to 90 per cent of patients have the abnormal protein migrating in the gamma globulin range, 25 per cent show a protein migrating between the gamma and beta range (the so-called "M" protein), and 15 per cent have the abnormal protein in the beta range. There have also been a few isolated reports of patients who had alpha-2 abnormal proteins. Dr. Jim,* who was at this hospital not long ago, was interested in studying both serum and urine electrophoretic patterns. He found that 60 per cent of a group of thirty-five patients with myeloma had abnormal serum patterns, while in this same group only about 25 per cent had Bence Jones proteinuria. Seven of his patients did not show hyperglobulinemia, but five of these had abnormal serum electrophoretic patterns. There were two patients who showed an abnormal protein pattern only in the

* JIM, R. T. S. An electrophoretic study of the abnormal proteins in urine, peripheral venous and bone marrow sera in multiple myeloma. *Blood*, 12: 56, 1957.

urine which points out the importance of performing an electrophoresis of the urine when the serum is normal. Other abnormal proteins found in this disease are cryoglobulins which precipitate out in the cold. They have been variously reported to occur in about 1 to 2 per cent of patients with multiple myeloma, but in some series the incidence has been as high as 6 per cent. On the other hand, of a group of patients who have cryoglobulinemia, more than 90 per cent will have multiple myeloma. Macroglobulins have occurred very rarely in multiple myeloma; in contradistinction to the cryoglobulins, if a series of patients with macroglobulinemia is studied, very few will have multiple myeloma.

DR. REINHARD: DR. Bricker, why do patients who have large amounts of Bence Jones protein in the urine usually have a normal total globulin level and vice versa?

DR. NEAL S. BRICKER: The only answer I could give would be a negative one. An obvious explanation would be that the excretion of Bence Jones protein accounts for the lack of globulin elevation. This is not a feasible answer, however, because the Bence Jones protein does not seem to be similar either chemically or electrophoretically to the abnormal serum globulin.

DR. REINHARD: Do you have anything to add to that, Dr. Moore?

DR. MOORE: There is good evidence now to indicate that these two abnormal proteins are synthesized at different rates and may be synthesized differently in different patients with the disease. Furthermore, when myeloma cells synthesize primarily Bence Jones protein rather than abnormal plasma globulin, the low molecular weight Bence Jones protein probably passes the glomerular filter more easily than the globulin.

DR. REINHARD: The very rapid sedimentation rate and the greatly increased rouleaux formation seen in multiple myeloma are well known phenomena. The *in vivo* equivalent of these phenomena is intravascular erythrocyte aggregation referred to in the literature as "I.E.A." Recently Marmont, Fusco, Gay and Mariotti* in Italy have made some observations on this phenomenon in twelve patients with proved myeloma. The plasma proteins were studied with Tiselius electrophoretic fractionation as well as by ultracentrifugation. In all twelve cases, the abnormal globulin fell into beta or gamma electrophoretic patterns; in no case was cryoglobulin or a macroglobulin demonstrated. The blood flow in the superficial vessels of the bulbar conjunctiva was observed in these patients by means of a Goldman biomicroscope with magnifications ranging from 40 to 88 times. *In vitro* the red blood cells clumped grossly on glass slides, regardless of whether the blood had been treated with oxalate, citrate, EDTA, or heparin. The studies of blood flow in the bulbar vessels in these patients showed several interesting phenomena. In the arterioles the blood had a somewhat more coarsely granular appearance than in the corresponding arterioles of normal subjects. In the capillaries, a "train" phenomenon was observed: cylindrical aggregates of red blood cells separated from each other by serum. Under direct microscopic observation, the blood was constantly moving forward, but in an irregular jerking fashion. When the blood passed through the capillary bed into the venules, this agglutination or aggregation was observed. There is no reason to doubt that a similar phenomenon occurs in the venules throughout the entire body in this disease. The aggregation is a striking *in vivo* counterpart of the phenomena that we can demonstrate in the laboratory by the sedimentation rate and the gross clumping of the red cells on glass slides. Indeed, all the patients in that study had very rapid erythrocyte sedimentation rates and gross aggregation of red cells on ordinary glass slides. When the myeloma red cells were added to normal plasma, there was no aggregation; but when normal red cells were added to the myeloma plasma, the same degree of clumping occurred as in the patient's own blood. This phenomenon, therefore, is a function of the abnormal proteins in the plasma rather than of the red blood cells. Furthermore, when normal saline was added to the blood, there was a rapid and complete dispersion of the aggregates. This is in striking contrast to what would occur if one added saline to a slide on which there were red cells agglutinated as a result of a direct immunologic mechanism. In other words, these cells are held together by a loose biophysical combination in a manner quite distinct from what happens with the immunologic mechanism of agglutination. When Hayem's solution was added to the blood instead of saline, there was again complete dispersion of the red cell aggregates; but in this

* MARMONT, A. M., FUSCO, F. A., GAY, A. and MARIOTTI, L. Intravascular erythrocyte aggregation ("sludged blood") in multiple myeloma. *Acta Haemat.*, 18: 49, 1957.

instance, a dispersion is due to the precipitation of the abnormal proteins by the Hayem's solution with resultant dissolution of the aggregate and flocculation of the abnormal proteins. The conjunctival sludging phenomenon correlated with the degree of *in vitro* flocculation. One would be tempted to suppose that intravascular hemolysis or intravascular occlusion due to thrombosis would be much more common in these patients than in normal subjects. Dr. Loeb, is there in fact any clinical evidence indicating an increased tendency to hemolysis or to thrombosis in patients who have myelomatosis?

DR. VIRGIL LOEB: In myeloma not complicated by the presence of cryoglobulinemia, the tendency to thrombosis is no greater than in the normal population; it is probably even less. Although the phenomena of sludged blood and erythrocyte aggregation are apparently very common, in these patients there is more of a tendency for purpura to develop than thrombosis. Because of the rapid flow in the arteriolar system, at least, true thrombosis rarely occurs.

DR. REINHARD: As Dr. Loeb has mentioned, actually the reverse of what one might anticipate is true. Dr. Lessner, how do you explain the fact that many patients with myeloma actually do have a bleeding tendency?

DR. HOWARD LESSNER: The several different mechanisms incriminated as the cause of bleeding in multiple myeloma might best be classified in four categories. The first, and probably most common mechanism, is that of thrombocytopenic bleeding due to bone marrow replacement by myeloma cells. The second type of bleeding is secondary to damage in the capillary walls caused by three factors. The first, and by far the most common, is that associated with the renal disease of multiple myeloma. The etiology of capillary damage in renal disease is poorly understood but is thought to be due to the accumulation of some unknown toxic substance. The second subclassification under this group is seen in para-amyloidosis in which infiltration of the small vessel walls with subsequent disruption of the vessels occurs. The third subcategory might be classified under cryoglobulinemia, with precipitation of cryoglobulin in the superficial vessels, subsequent thromboses and, on rewarming, hemorrhage. The third general classification would be myeloma with elevated globulins which may cause increased difficulty with intrinsic blood coagulation mechanisms. Coagulation studies carried out on these patients have shown that thromboplastin formation is normal and that prothrombin conversion is normal. However, Craddock* has reported a defect supposedly in the conversion of fibrinogen to fibrin; when thrombin is added to the plasma of a patient with myeloma, a gel rather than a fibrin clot is formed. Craddock thought that this abnormal reaction was due to a deficiency in ionizable calcium, with the calcium being bound by the abnormal protein. He further showed that when calcium is added *in vitro* to the gel, a good fibrin clot is formed. The fourth and final category is probably the least frequent and represents a deficiency in various coagulation factors secondary to hepatic involvement.

DR. REINHARD: I would now like to focus your attention on the effect of multiple myeloma on the resistance of the host to infection. It is an old clinical observation that patients with myelomatosis seem to be unusually susceptible to infection. For example, a recent article in the Danish Medical Bulletin by Killmann and Knudsen† reports observations on a sixty-nine year old man with myeloma diagnosed in 1952. This patient had no demonstrable bronchiectasis or other pre-existing lung disease, but from 1952 to 1955 he had nine attacks of pneumonia. After penicillin was administered prophylactically, he had fewer attacks of pneumonia. Dr. Harford, do you agree that these patients have a lowered resistance to infection? And if so, to what types of infection are they particularly susceptible?

DR. CARL HARFORD: I certainly do agree and have the impression that pneumococcal infection is especially frequent. In my experience such patients may have recurrent pneumococcal infection including meningitis, bacteremia and arthritis.

DR. REINHARD: Zinnemann and Hall‡ studied sixty-four patients with multiple myeloma; ten of these patients had recurrent pneumonia, mostly pneumococcal pneumonia. These ten patients had a total of forty-four attacks of pneu-

* CRADDOCK, C. G., JR., ADAMS, W. S. and FIGUEROA, W. G. Interference with fibrin formation in multiple myeloma by an unusual protein found in blood and urine. *J. Lab. & Clin. Med.*, 42: 847–859, 1953.

† KILLMANN, S. A. and KNUDSEN, E. E. Recurrent pneumonia in multiple myeloma due to acquired functional hypogammaglobulinemia. *Danish M. Bull.*, 4: 153, 1957.

‡ ZINNEMANN, H. H. and HALL, W. H. Recurrent pneumonia in multiple myeloma and some observations on immunologic response. *Ann. Int. Med.*, 41: 1152, 1954.

monia with the individual patients having from two to thirteen bouts each. The concept has been advanced that patients with myeloma are inadequate antibody formers even though they may have very large amounts of globulin. Dr. Brittingham, would you comment on this relationship?

DR. THOMAS BRITTINGHAM: Patients with myeloma do have a tremendous susceptibility to infection, and patients who have recurrent pneumonia should even be suspected of having multiple myeloma. The reason for this susceptibility is by no means completely known. Several recent studies have demonstrated that patients with myeloma generally show a poor antibody response to antigenic stimulation. Larson concluded that a deficiency of circulating antibody appears to be a consistent and characteristic feature of myelomatosis. In nine cases of myeloma, apparently selected at random, he found that six patients had no red cell isoagglutinins whatsoever, and two others had very low levels. It has also been suggested but not proved that the antibody response of a patient with myeloma becomes increasingly poor as his globulin becomes higher. The deficiency of circulating antibody or normal gamma globulin in myeloma has been so impressive that recently a special method has been reported for the demonstration of secondary hypogammaglobulinemia in the presence of abnormal myeloma protein migrating as a gammaglobulin. We should conclude by saying that there are undoubtedly other mechanisms responsible for the increased susceptibility of patients with myeloma since almost all such patients have a poor antibody response and yet perhaps only a quarter of them show recurrent infection.

DR. REINHARD: There is some indication also of an inverse ratio between the antibody response and the amount of abnormal serum proteins present in the serum; that is, the response is poorer in the patients who have a large amount of abnormal globulins in the serum than in those patients with myeloma who do not have a markedly elevated abnormal globulin level.

DR. SOL SHERRY: Another reason for the frequent incidence of pneumonia may be the hypoventilation which results because of fractured ribs, disability and such local causes.

DR. REINHARD: Dr. Bricker, would you discuss this patient's renal failure?

DR. BRICKER: It is well known that renal insufficiency is common in multiple myeloma, and probably occurs in at least a quarter of the patients with this disease. With one exception, which will be mentioned in a moment, the changes in renal function are not specific, and typically the progressive renal insufficiency develops. Hematuria and hypertension are infrequent. The term " myeloma kidney" which is widely used, probably warrants no specific pathologic connotation because the lesion is so often a mixed one. With regard to the possible pathogenesis of the renal failure, there is considerable controversy. Many observers believe that the filtration of large amounts of protein into the tubular lumen and the inspissation of this protein material with cast formation in the distal tubule is associated causally with the development of a nephropathy. These observers believe moreover that Bence Jones protein may have a specific nephrotoxic property and point to the fact that frequently giant cells may be found around the casts and in the tubular epithelial cells. I think that this is not by any means universally accepted, and although widespread occlusion of tubular lumens obviously contributes to renal insufficiency, it is not fair to conclude that the occlusion is the major cause of renal failure in myeloma. Several other factors may contribute. Hypercalcemia has been mentioned as a frequent accompaniment of multiple myeloma. In any patient with hypercalcemia, whether it be due to myeloma or any other cause, the kidney may sustain devastating consequences. These are threefold: (1) nephrolithiasis, which I believe is rare in myeloma; (2) nephrocalcinosis, which may occur in myeloma, and (3) the development of rapid renal insufficiency in which neither stones nor calcium crystals are demonstrable.

DR. REINHARD: Would you like to express an opinion on whether or not this patient has nephrocalcinosis?

DR. BRICKER: The dense appearance of the kidneys on x-ray makes calcinosis a likely possibility. I think that we have to assume that this patient's calcium may have been much higher than the recorded value prior to the time that his phosphate became elevated due to renal insufficiency. Now let me briefly mention some of the other renal lesions in multiple myeloma, and then I will consider what might be found in this patient. Sludging in the glomerular capillaries has also been noticed similar to the sludging in the conjunctival vessels, and in some instances sclerosis of glomeruli and basement

membrane thickening has been found. The vessels are frequently arteriosclerotic. Rarely there may be infiltrates of myeloma cells in the kidneys. The presence of para-amyloidosis has been described in this disease also. Just for completeness sake, one additional point should be made. There have been perhaps twenty cases of adult Fanconi syndrome reported in the literature to date. In three of these, the patients have had multiple myeloma. There has been some suggestion that there might be a cause and effect relationship.

With regard to the present patient, I think he will have widespread morphologic changes in his kidneys and that he will have the casts associated with myeloma. These will probably be eosinophilic and perhaps laminated and there may be surrounding giant cells. In addition, because of the history of the acute pyelonephritis three months before admission, he may very well have evidence of chronic persisting pyelonephritis. Finally, there may be nephrocalcinosis. The history of hypertension is unclear. He was normotensive on admission; his retinal vessels were normal; and I do not think we can conclude that he will have advanced nephrosclerosis.

DR. MOORE: Dr. Reinhard, may I ask Dr. Bricker a question? He pointed out that in about 25 per cent of the patients with myeloma so-called myeloma nephropathy develops. Many students of the disease, however, have thought that the relationship between Bence Jones proteinuria and renal failure from myeloma kidney was somewhat better than that. Among patients with persistent Bence Jones proteinuria, therefore, the incidence of renal failure might be considerably higher.

DR. BRICKER: Dr. Moore, there appears to be disagreement in the literature about this point. In several studies, the authors were not able to detect Bence Jones proteinuria in much more than 40 to 50 per cent of cases.

DR. LILLIAN RECANT: May I add just one comment? I noticed that the uric acid level was elevated to 7.5 mg. per cent when he was treated with urethane. Subsequently he had a very acid urine that was pH 4.5. There is the possibility of an additional potential renal insult from uric acid crystals.

DR. REINHARD: That is a good point. Dr. Bricker, it would be of interest to have you discuss your recent attempt to take advantage of the apparent lowered antibody responses these patients show to foreign protein-antigen in the treatment of advanced renal failure by homotransplantation of the human kidney. Would you just go over this briefly?

DR. BRICKER: We were recently presented with a unique opportunity that could not have been created in the laboratory. A patient with advanced myeloma became hypotensive following what was presumed to be a gram negative septicemia, and thereafter acute tubular necrosis developed. Because of the antibody problems that patients with myeloma have, and because of the firm convictions of many that the major reason for rejection of homotransplanted tissue is immunologic distinction, it was believed that a transplanted kidney might survive, at least temporarily in this patient. If the transplant could function for a period of seven to ten days, it might prolong the patient's life sufficiently to allow his own renal tubular epithelial cells to regenerate. We did not believe it was justified to take a kidney from a living person, and so the kidney was obtained from a patient who entered the emergency room of this hospital with a myocardial infarct and died. After the decision was made to perform this transplantation, it took seventy-two hours to find this suitable donor. Once the donor was found, the transplantation was performed. The patient, however, was then moribund. The kidney was transplanted into the thigh by Dr. Falls Hershey (no anesthesia was required); an hour and fifty minutes after the death of the donor the circulation to the transplanted kidney was successfully re-established and the ureter filled with urine. Unfortunately, the patient died at this time presumably due to factors related to his underlying uremia.

DR. REINHARD: This is really a fascinating attempt to apply physiologic principles to a desperate situation. The patient's critical terminal state, I suppose, doomed the trial to failure before it started. Lastly, Dr. Daughaday, would you discuss briefly the disturbed calcium metabolism of this disease, and tell us whether or not you think our patient had any type of parathyroid abnormality.

DR. DAUGHADAY: The abnormalities usually observed are hypercalcemia usually with a normal or somewhat elevated serum phosphorous level in the absence of renal disease. The cause of hypercalcemia may relate in part to the elevated proteins with increased binding of calcium. However, the calcium ion level is also elevated so that binding is not the only explanation.

Metastatic calcification is seen and was noted in this particular patient in the arteries and perhaps in the kidneys. Actually the degree of binding of calcium to the abnormal serum proteins is not high, so that in most of these patients, the major explanation for hypercalcemia is a rather obscure mobilization of bone minerals which may be somewhat independent of the actual areas involved with myeloma. I cannot go very much farther except to say that the differential diagnosis of myeloma with or without hyperparathyroidism is extraordinarily difficult. In one of our patients with a renal stone, we were quite content with the diagnosis of multiple myeloma as the cause for his hypercalcemia. He died with myeloma plus hyperparathyroidism. It is virtually an impossible differential diagnosis at the present time. So although the myeloma is an adequate explanation of hypercalcemia there perhaps is the suggestion that parathyroid abnormalities occur more frequently than would be expected.

DR. REINHARD: Dr. Berg, I suppose the terminal convulsion has no specific significance and can be explained entirely on the basis of the functional nervous system disturbance due to a combination of anoxia, hypotension and abnormal chemical composition of the body fluids. Is this in keeping with your concept?

DR. LEONARD BERG: I think that is correct. There is no reason to believe that he had any specific brain lesion. He seemed from the protocol to be reasonably alert until he had a convulsion and suddenly died. Sudden death does not generally come from the brain, and one would be more tempted to look to the heart for a cause.

DR. SOL SHERRY: This patient may have fairly extensive deposits of para-amyloid. Patients with Bence Jones protein in the urine and normal serum globulin are the type in whom we tend to see amyloid deposits. In addition, there is cardiac enlargement, a certain amount of ecchymosis and considerable muscle weakness. These all might be associated with a type of amyloidosis which is similar in distribution to primary amyloid.

DR. REINHARD: The final diagnoses are multiple myeloma, uremia due to multiple pathologic disorders in the kidneys, probably including renal calcinosis, obstruction of renal tubules by proteinacious material, possibly pyelonephritis (although we have little to suggest this except that these patients have a lowered resistance to infection). The problem of the parathyroid disturbance has been discussed by Dr. Daughaday and I have nothing to add. I agree with Dr. Sherry that there is a high probability of para-amyloid involvement. The gross findings will be presented by Dr. Grisham.

PATHOLOGIC DISCUSSION

DR. JOE W. GRISHAM: A small amount (50 ml.) of slightly bloody fluid was observed in the abdomen of this 81 kg., slightly obese white man. Several foci of fat necrosis were present in the retroperitoneal tissue and in the fat around the pancreas. The pancreas was swollen and hemorrhagic. Ecchymotic areas were also present in the retroperitoneal tissue around the pancreas. The main pancreatic duct entered the common bile duct in the distal portion of the ampulla of Vater and was not obstructed or distended. The gallbladder contained fifteen mixed stones. The biliary ducts were normal in size and did not contain stones. The kidneys weighed 125 gm. each, and appeared smaller than normal. The renal capsules were slightly thickened and stripped with some difficulty but the cortical surfaces were smooth and pale. On cut section, the renal cortex was moderately decreased in size and the entire cortex and medullary portions had a pale waxy appearance. A small amount (50 ml.) of pleural fluid was present in the right pleural space. The lungs were congested and weighed 1,080 gm. The heart was slightly enlarged (400 gm.) and on cut section several small yellowish foci were observed in the myocardium. The endocardium of the left ventricle was slightly thickened. Only a moderate degree of arteriosclerosis was present in the coronary arteries. The cancellous bone was extremely soft in all the areas which were examined. The vertebral bodies of the eleventh and twelfth thoracic and second lumbar vetebrae were narrowed. An ill-defined area of destruction of cancellous bone was evident in the second lumbar vertebra. A nodular enlargement of the right sixth rib posteriorly was present. This apparently represented a deformity of an old fracture. The brain, spinal cord and the remainder of the visceral organs appeared normal on gross inspection.

DR. PAUL E. LACY: Microscopically, a diffuse infiltration of myeloma cells was present in the bone marrow with only a few foci of hemopoiesis remaining. The infiltrating cells had eccentric

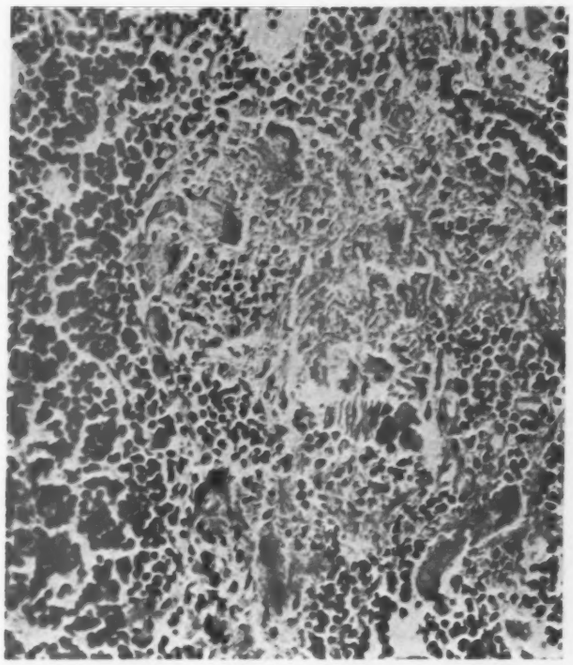


FIG. 1. A nodular accumulation of myeloma cells in the bone marrow is illustrated. Dense, eosinophilic hyaline material is present within the center of the myeloma cells. The hyalin did not react specifically with stains for amyloid. Hematoxylin and eosin stain, magnification approximately ×100.

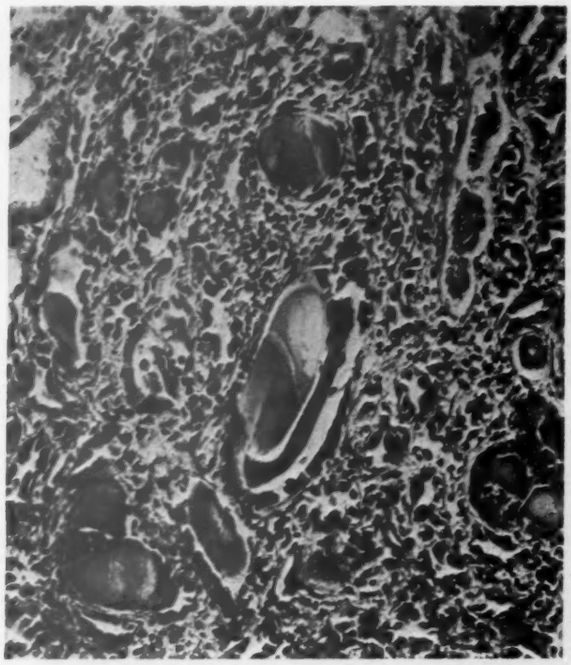


FIG. 2. A foreign body giant cell surrounding a cast in a renal tubule is illustrated. The surrounding tubules are atrophic and a chronic inflammatory reaction is present in the interstitial tissue. Hematoxylin and eosin stain, magnification approximately ×100.

nuclei with a paranuclear clear zone and resembled typical plasma cells. In some areas, nodular accumulations of myeloma cells were present and the central portion of these areas contained an eosinophilic hyaline substance. (Fig. 1.) This material resembled amyloid or para-amyloid but a positive identification was not established since a negative reaction was obtained with several different amyloid stains. In the kidney, the renal tubules were atrophic and many contained densely eosinophilic casts. Foreign body giant cells were observed surrounding the casts in some areas. (Fig. 2.) This foreign body reaction to the casts is a typical change in multiple myeloma. Presumably, these casts are composed of Bence Jones protein. A few neutrophils were present around some of the casts and a slight focal neutrophilic infiltration was observed in the interstitial tissue in other areas. A moderate degree of fibrosis and chronic inflammatory reaction was also present in the interstitial tissue. Nephrocalcinosis was not present. In the heart, some of the small branches of the coronary arteries contained large masses of hyaline which partially occluded the lumen of these vessels. (Fig. 3.) This material resembled amyloid but specific stains for this substance were negative. Focal areas of acute infarction of the myocardium were observed microscopically. The myocardial fibers were smudged in these areas and inflammatory cells were not seen.

A diffuse, acute hemorrhagic pancreatitis was evident. Large areas of necrosis which were bounded by a rim of intact acinar cells and neutrophils were present throughout the pancreas. (Fig. 4.) Necrosis of the vascular walls with thrombosis and interstitial hemorrhage had also occurred. The etiology of the pancreatitis was not determined. A common channel for the pancreatic and common bile duct was present but no evidence of calculi was observed in this area. The necrosis and thrombosis of the pancreatic vessels was probably secondary to the pancreatitis. It is quite evident that the acute pancreatitis did play a significant role during the last two or three days of this patient's hospital course. In summary, the pathologic changes observed were those of multiple myeloma with associated renal changes as well as the development of an acute hemorrhagic pancreatitis during the terminal course of his illness.

The final anatomical diagnoses are multiple

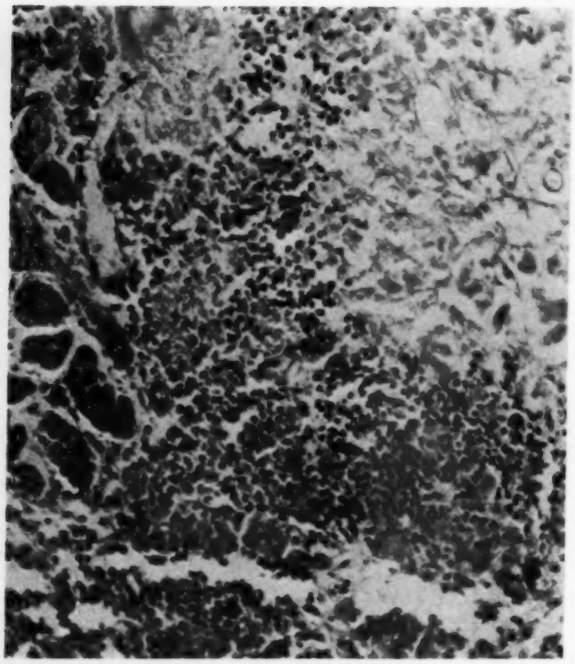


FIG. 3. A large hyaline mass which almost replaces the wall of a coronary artery is illustrated. The hyaline did not react with specific stains for amyloid. Hematoxylin and eosin stain, magnification approximately ×100.

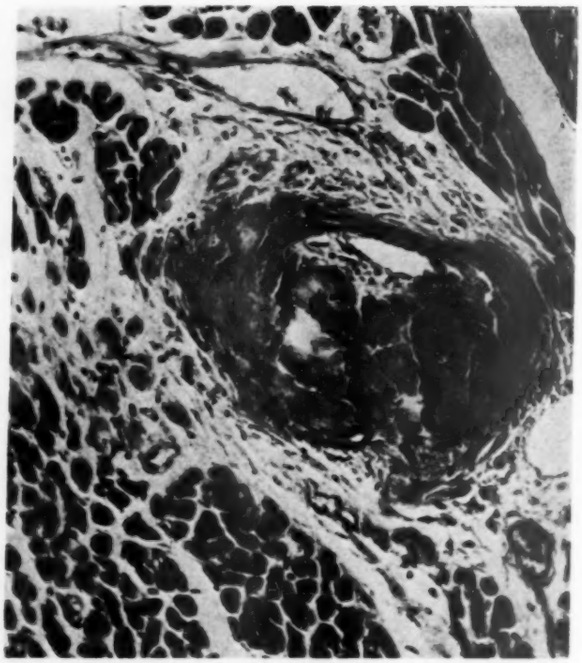


FIG. 4. The necrotic pancreatic cells are surrounded by a rim of neutrophiles and a few intact acinar cells. Hematoxylin and eosin stain, magnification approximately ×100.

myeloma with generalized osteoporsis, slight compression fractures of the D_{11}, D_{12}, and L_2 vertebral bodies and the right sixth rib; nephrosis of multiple myeloma (history of uremia); arteriolar nephrosclerosis, moderate; acute focal pyelonephritis; fibrinous pericarditis, slight; acute hemorrhagic pancreatitis with widespread focal fat necrosis; thrombi in peripancreatic veins, multiple; fatty metamorphosis of the liver, advanced; focal areas of recent micro infarcts of the myocardium; focal fibrosis of the myocardium; atelectasis of the lower lobes of the lungs; congestion of the lungs; bronchopneumonia, slight (gram positive cocci seen in section); acute colitis; and hemosiderosis of the spleen, moderate.

The accessory diagnoses are arteriosclerosis of the aorta, moderate; of the coronary arteries, moderate; of the cerebral arteries, slight; of the renal, hepatic, superior mesenteric arteries, moderate; of the splenic artery, slight; sclerosis of the anterior leaflet of the mitral valve; fibroelastic thickening of the endocardium of the left ventricle, slight; calcified nodule in the upper lobe of the left lung; calcified left hilar lymph nodes of the lung; calcified nodules in the spleen (1 mm.), multiple; increased fibrous tissue in the spleen; cholelithiasis, fifteen small (0.5 cm.) mixed stones; and surgical absence of the appendix.

DISCUSSION

DR. REINHARD: Were the parathyroids examined?

DR. LACY: Yes, they were not unusual.

DR. CHARLES PARKER: It might be worth a brief comment on the focal myocardial necrosis and pancreatitis with local venous thrombosis in this patient. Similar pathological changes are described in fatal hyperparathyroidism in man and animals.* In most of the fatal cases in patients with these changes serum calcium levels have exceeded 16 mg. per cent. In this patient the hypercalcemia was not this marked. However, it may be that a more striking degree of hypercalcemia was present before hospitalization and that terminal values were modified by the severe renal failure and development of acute pancreatitis. It is not known whether or not the pathological features found at autopsy in patients with severe primary hyperparathyroidism are due to hypercalcemia

* THOMAS, W. C., JR., WISWELL, J. G., CONNER, T. B. and HOWARD, J. E. Hypercalcemia crisis due to hyperparathyroidism. *Am. J. Med.*, 24: 229–329, 1958.

per se or to some action of the hormone in addition to its effect on calcium mobilization. Certainly many of the clinical features of severe hypercalcemia due to causes other than hyperparathyroidism correlate well with the picture seen in so called parathyroid crisis. Areas of myocardial inflammation and degeneration without calcification have been described in experimental vitamin D intoxication in rabbits.* One is tempted to wonder whether or not the severe hemorrhagic pancreatitis found in this patient could be related in some way to the hypercalcemia.

* Hass, G. M., Trueheart, R. E., Taylor, B. and Stumpe, M. An experimental histologic study of hypervitaminosis D. *Am. J. Path.*, 34: 395–431, 1958.

Case Report

Chronic Pericardial Effusion in Brothers, with a Note on "Cholesterol Pericarditis"*

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Baltimore, Maryland

THE two patients described in this report are brothers who were found to have unusual asymptomatic chronic pericardial effusions. Of particular interest was the discovery of cholesterol crystals in the pericardial effusion in one of the brothers. Both patients were independently discovered to have large heart shadows on routine x-ray survey films. The second case was detected three years after the first. No other instance of pericardial disease has been found in the immediate family.

CASE REPORTS

CASE I. F. Y. (JHH 577282), a seventeen year old white high school boy, resident of Maryland, was seen for the first time on June 27, 1951. In April 1951 a routine chest x-ray film had disclosed a greatly enlarged cardiac shadow. In the autumn of 1950 the patient recalled having had a grippe-like illness characterized by cough, slight malaise and mild headache but he was not ill enough to miss his classes, and several of his classmates had experienced similar symptoms. Except for a brief episode of sticking pain in the right upper side of the chest, which was aggravated by deep breathing and relieved by an ice bag, about three weeks prior to his visit the patient had been quite well. His past health had been entirely uneventful.

The family history seemed quite without relevant findings. His mother had died of complications of an operation for appendicitis. One brother had been killed in action in World War II. Three brothers and four sisters were in good health at that time (1951).

Physical examination revealed a suntanned, robust young man who was neither ill nor uncomfortable. At no time during observation was there any fever. His blood pressure was 120/80 mm. Hg; pulse was 75 and regular. There were no signs of heart failure. The skin, mucous membranes, glandular system, abdominal, neurological and skeletal examinations were quite normal. The precordium was quiet save for a faint pulsation noted in the third and fourth interspace 6 cm. to the left of the mid-sternal line. The cardiac dullness was greatly increased both to the right and left, the left border of dullness being in the anterior axillary line in the sixth interspace. The cardiac sounds were slightly muffled but were otherwise normal. No murmurs or frictions were noted.

Initial x-ray and fluoroscopic studies disclosed a huge globular cardiac shadow with the left border almost reaching the chest wall in the posteroanterior projection. Pulsations were diminished. The base of the heart was of normal width. Hilar and parenchymal vascular markings in the lung fields were all normal. (Fig. 1.) Initial electrocardiogram (July 11, 1951) showed low T waves in all leads and a P-R interval of 0.16 seconds. Several urinalyses showed a specific gravity varying between 1.018 and 1.030 without albumin, sugar or abnormalities in the centrifuged sediment. A serologic test for syphilis was negative. Several stool examinations for parasites and occult blood were negative. Between July 9 and July 28, 1951, repeated blood studies showed a hematocrit varying between 51 and 55 per cent, icterus index of 3 to 8, sedimentation rate of 2 to 5 mm. (Wintrobe). The white blood count was 6,550 per cu. mm. on admission with 3 per cent juvenile neutrophils, 70 per cent polymorphonuclear neutrophils, 2 per cent eosinophils, 19 per cent lymphocytes and 6 per cent momocytes, with normal platelets. Subsequent white blood counts were 8,800 to 12,100 per cu. mm. with essentially unchanged differential count. Blood chemical studies revealed non-protein nitrogen 44 mg. per 100 ml., sugar 104 mg. per 100 ml., cholesterol 190 mg. per 100 ml. (subsequently 234 and 243 mg. per 100 ml.), phosphorus 4.1 mg. per 100 ml., alkaline phosphatase 7.3 Bodansky units, total serum proteins 7.3 gm. per 100 ml., with albumin 4.8 gm. and gobulin 2.5 gm. per 100 ml. The cephalin flocculation test was negative and the thymol turbidity 2.8 units. The bilirubin was 1.4 mg. per 100 ml. total, with 0.8 mg. per 100 ml. direct. The venous pressure was 160 mm. (later 105 mm.) of water, and the circulation time with Decholin® was eighteen seconds,

* From the Department of Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland.

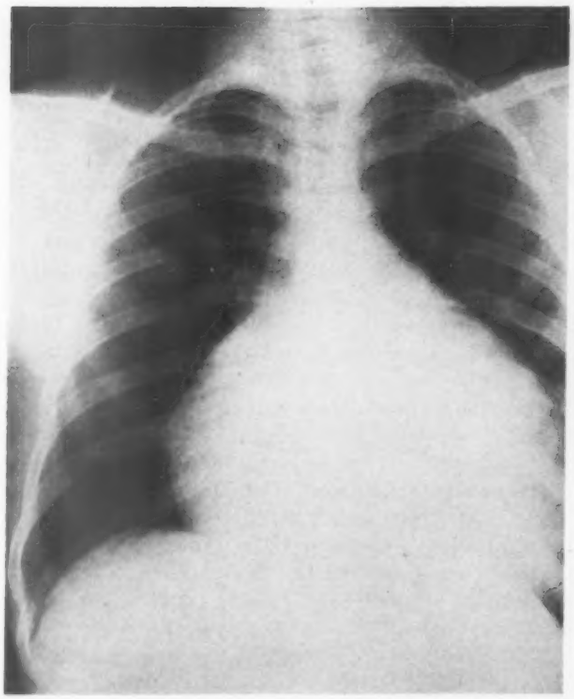


FIG. 1. Posteroanterior chest roentgenogram of patient F. Y. (Case 1), July 11, 1951.

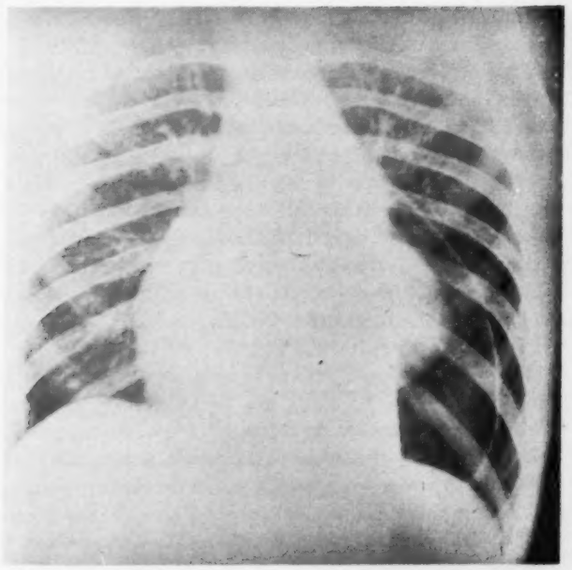


FIG. 2. Posteroanterior chest roentgenogram of patient F. Y. (Case 1) taken after pericardial aspiration and air instillation (July 17, 1951). The film was exposed with the patient lying on his right side and demonstrated a fluid level and a delicate pericardial wall.

subsequently 12 seconds. There was a positive skin test to "old tuberculin" at a dilution of 1:100,000.

On July 13, 190 ml. of a cloudy, yellow, satiny shimmering fluid were removed from the pericardial cavity through the subxiphoid approach. The fluid had a striking appearance, similar to a suspension of gold paint. If left undisturbed it looked like ordinary opalescent amber pleural fluid but when flowing or shaken a spangled scintillating appearance was noted in the eddying fluid. The specific gravity was 1.020. Under the microscope crystals with notched corners, typical of cholesterol crystals, were seen. Only an occasional white blood cell was noted, including some rather large cells with highly refractile round granules. The protein content was 6.4 gm. per 100 ml., sugar 84 mg. per 100 ml. The cholesterol content of the supernatant fluid was 85 mg. per 100 ml. and of the total fluid, 162 mg. per 100 ml. The total lipids were 0.33 gm. per 100 ml. Routine cultures (including special examinations for brucella and for acid-fast bacilli) and guinea pig inoculation failed to reveal any organisms. A cell block of the centrifuged sediment showed no tumor cells.

On July 17, 1,000 ml. of similar fluid was removed and 400 ml. of air injected into the pericardium. X-ray studies were made immediately following this procedure, demonstrating a thin, delicate pericardial sac without evidence of tumor or cyst in any of the projections. (Fig. 2.) On this occasion 22 white cells and 891 red cells per ml. were counted. Repeat studies including culture for acid-fast bacilli were again negative. The patient had another pericardial tap performed on July 26 at which time 600 ml. of similar fluid was removed. This fluid contained 2,340 cells per cu. mm. with a differential count of 46 per cent polymorphonuclear neutrophils, 14 per cent eosinophils and 40 per cent mononuclear cells. Following the initial demonstration of cholesterol crystals in the pericardial fluid the thyroid function was carefully evaluated despite the absence of clinical evidences of thyroid disease. The basal metabolic rate was minus 11 per cent. The serum cholesterol ranged between 190 and 243 mg. per 100 ml. An I^{131} tracer study revealed a normal uptake by the thyroid gland.

The patient was discharged from the hospital on July 28, 1951, with a diagnosis of "cholesterol pericarditis, cause unknown." Since there were no symptoms and since no definite etiology for the pericarditis had been established it was decided to observe the patient at home for a while. While at home he continued normal activities without exercise. His appetite remained excellent. He had no chills, sweats, cough, chest pain or any symptoms suggestive of heart failure.

On September 10, 1951, he was readmitted to The Johns Hopkins Hospital for re-examination. His temperature, pulse and respirations were normal. The blood pressure was 100/60 mm. Hg. The physical examination seemed exactly as noted on his previous admission two months earlier. Repeat laboratory studies showed a red blood cell count of 6.54 million per cu. mm., hemoglobin of 18 gm. per 100 ml. and a hematocrit of 56 per cent. The icterus index was 5 and corrected sedimentation rate was 4 mm. per hour. On

September 13 the hematocrit was 51.2 per cent. The platelets were 248,000 per cu. mm. On September 21 the red blood cell count was 6.21 million per cu. mm., hemoglobin was 17.5 gm. per 100 ml. and hematocrit was 52 per cent. The white blood cell count varied between 7,100 and 8,550 per cu. mm. The serum nonprotein nitrogen was 41 mg. per 100 ml., sugar 88 mg. per 100 ml., cholesterol 217 mg. per 100 ml., serum albumin 4.8 gm. and globulin 2.8 gm. per 100 ml. Repeat x-ray studies showed that the cardiac outline was considerably larger than the last film taken prior to his previous discharge on July 27, 1951, although smaller than on July 13, 1951.

It was clear that he had reaccumulated a considerable volume of fluid in his pericardium. Electrocardiogram showed no change from his previous record. During this hospitalization a pericardial tap was performed on two occasions, with the removal of 600 ml. the first time and 300 ml. the second time. On both occasions the fluid was noted to be less cloudy than previously. The cholesterol content was 160 mg. per 100 ml. with an albumin of 4.1 and globulin of 2 gm. per 100 ml. Cholesterol crystals were no longer noted. Because of the unusually high hematocrit and red blood cell count, the patient had pulmonary function studies performed in Dr. Richard Riley's laboratory. These revealed normal ventilation, dead space, venous admixture and diffusing capacity. It was concluded that the polycythemia was not related to any difficulty of oxygen transport. The patient was discharged on September 23, 1951.

When seen again on November 9, 1951, he had apparently reaccumulated a large amount of fluid in his pericardium. On November 10, 600 ml. of pericardial fluid was aspirated. The fluid was straw-colored and slightly less turbid than on previous occasions. The specific gravity was 1.018, there were 100 cells per cu. mm., the cholesterol content was 167 mg. per 100 ml. and the total protein was 5.9 gm. per 100 ml. Again cultures for acid-fast bacilli were negative. Special cultures for fungi were likewise negative. The patient was discharged to remain at home on modified bedrest although he continued to have no symptoms and no complaints.

He was admitted to the hospital for a two-day period in January 1952, at which time the heart shadow was noted to be approximately the same size as on November 12, 1951. An attempt was made to obtain fluid from the pericardium on this occasion without success. The old tuberculin skin test was repeated and again found to be strongly positive. The electrocardiogram showed very slight inversion of T-1. When seen in March and June 1952, he had no chest pain, fever, shortness of breath or any other distress. His cardiac and x-ray findings remained unchanged.

After more than a year of observation, on August 7, 1952, the patient was operated upon by Dr. Alfred Blalock. With the patient lying on his back, an anterolateral incision was made on the left. The left lung appeared normal. There were no enlarged mediastinal nodes. A good deal of fluid was noted inside the pericardial cavity but there was no evidence of a cyst. An incision was made in the pericardium anterior to the left phrenic nerve and approximately 200 ml. of clear yellow fluid escaped. The pericardium was noted to be only slightly thickened and not adherent to the epicardium at any point. The heart was noted to pulsate well at every point. The epicardium was very slightly thickened. A few very small hard yellowish masses, about 1 mm. in size, were attached to the epicardium and were thought to be cholesterol deposits. There was no evidence of a mediastinal node rupturing into the pericardial cavity.

About four-fifths of the parietal pericardium was then removed including the portion attached to the diaphragm. Microscopic examination showed very mild, scattered chronic inflammation in the wall of the pericardium with scattered round cell foci. A tiny nodule which had been thought grossly to be a cholesterol deposit was found to be an encapsulated hematoma about 1 mm. in diameter, probably the site of previous needle puncture. There was no evidence of tuberculosis.

The patient's postoperative course was uneventful. When seen on September 17, 1952, his temperature was 99.2°F., pulse 108 and blood pressure 120/70 mm. Hg. The operative incision was well healed, the heart was normal in size to percussion, and the left border of dullness was 9 cm. to the left of the mid-sternal line. The heart sounds were quite loud and no accentuation or murmurs were noted. An occasional third heart sound was heard. An x-ray taken on September 10, 1952, showed clear lung fields. The over-all cardiac size was normal but the contour was slightly unusual in that the left border appeared to have been displaced upward and laterally, with a clear area of lung visualized just below the apex. Fluoroscopy revealed normal cardiac pulsations. At this time the patient was permitted to return to full activity at school and he entered barber-training school.

The patient has been seen repeatedly since that time and he has remained entirely well. He has gained approximately 30 pounds in weight and when last seen on January 22, 1957, weighed 191 pounds. Repeated blood counts have revealed varying degrees of polycythemia. The red blood cell count on March 22, 1951, was 6.29 million per cu. mm., hemoglobin 17.2 gm. per 100 ml., hematocrit 54.8 per cent, white blood cell count 10,000 per cu. mm. On January 24, 1955, his red blood cell count was 6.19 million per cu. mm., hemoglobin 16.8 gm. per 100 ml., hematocrit 52 per cent, white blood cell count 9,650 per cu. mm. On January 22, 1957, the hematocrit was 52.5 per cent and the hemoglobin 17.5 gm. per 100 ml.

On January 22, 1957, the blood pressure was 120/70 mm. Hg and pulse 68. He was noted to be ruddy-faced and obese. His eye grounds showed striking

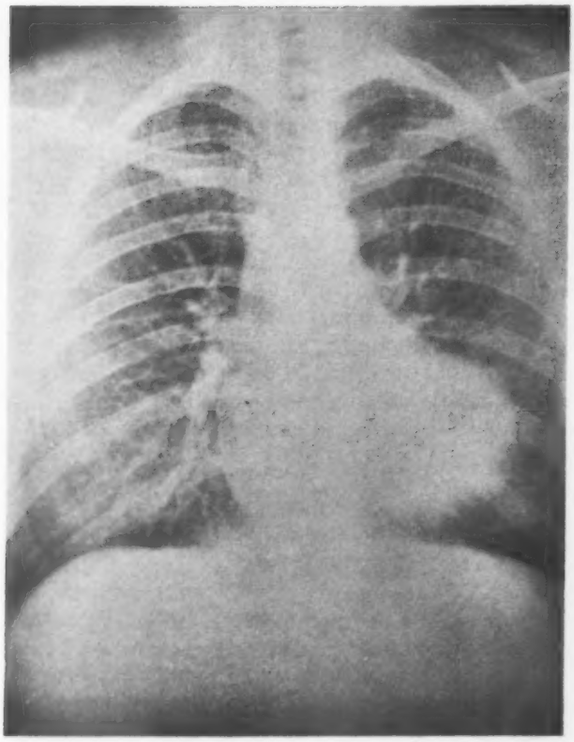


FIG. 3. Postoperative chest roentgenogram of patient F. Y. (Case 1), January 22, 1957.

retinal shimmer and slightly tortuous blood vessels. The remainder of the physical examination was entirely normal. Fluoroscopy and x-ray of the chest revealed a snub-nosed contour of the heart with a normal over-all cardiac size. (Fig. 3.) The electrocardiogram showed a double R wave in V_1 and striking T wave inversion in leads V_1 through V_4 with a diaphasic TV_5. (Fig. 4.) These changes are thought to represent residual damage in the superficial layers of myocardium, possibly due to loss of pericardium or adhesions of the heart to the pleura.

CASE II. W. Y. (JHH 673999), the second patient, was first seen on May 24, 1954, at the age of twenty-four. He is an older brother of the first patient and is employed as a telephone lineman. He was referred because of the finding of a large heart shadow on a routine chest x-ray which had been taken one week previously. A chest x-ray in 1952 was said to have been normal. The patient had always performed heavy physical work without symptoms. In the week since the x-ray had been taken he had become aware of a dull feeling in the left upper side of the chest which was intermittent and not particularly disabling. He did not recall having had any recent or remote infections or injuries. In the preceding three years he had gained approximately 30 pounds in weight. A slight early morning cough productive of a small amount of clear sputum was attributed to the smoking of cigars.

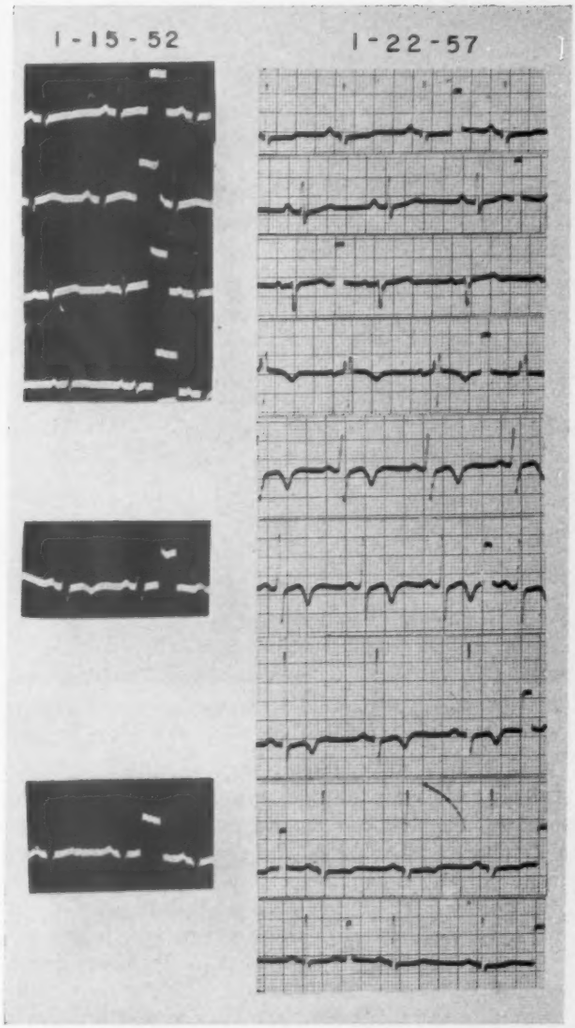


FIG. 4. Electrocardiograms of patient F. Y. (Case 1). The record on the left, January 15, 1952, is a preoperative tracing (leads 1, 2, 3, V_1, V_2 and V_5). The record on the right, January 22, 1957, is postoperative (leads 1, 2, 3, V_1–V_6).

Physical examination disclosed an exceptionally husky, ruddy-faced, muscular young white man who did not look in the least ill. His temperature was 98.6°F., pulse 60 and regular, height 71½ inches, weight 210 pounds and blood pressure 140/90 mm. Hg. No paradoxical pulse was noted. A blush was noted on the left side of the forehead, the right side of the upper anterior thorax, right shoulder and right arm. The optic fundi revealed strikingly tortuous retinal arterioles with localized constrictions and increase in the shimmer together with some compression at the arterial-venous crossings. There were no hemorrhages or exudates and no papilledema. The neck veins were not distended, the liver was not palpable and there was no peripheral edema. The examination of the lungs was normal. There was no precordial pulsation.

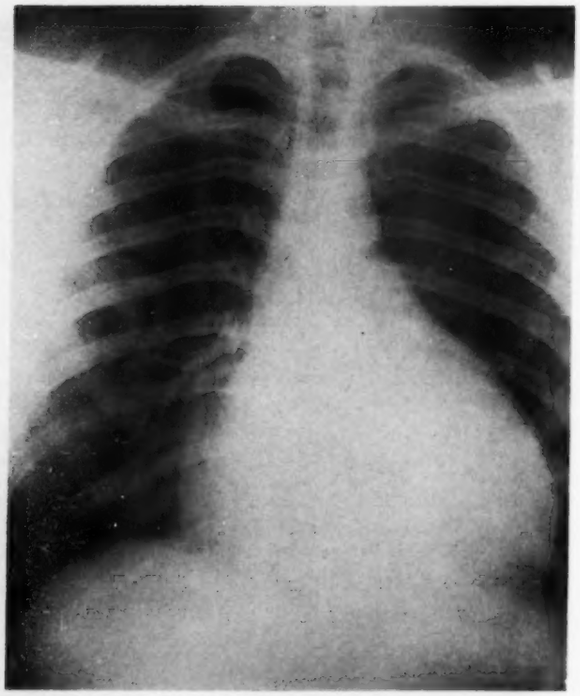


FIG. 5. Posteroanterior chest roentgenogram of patient W. Y. (Case II), May 24, 1954.

The area of cardiac dullness was greatly increased to the left. The left border was noted in the anterior axillary line in the fifth and sixth interspaces. The cardiac dullness extended 3 cm. to the right in the fourth interspace. The heart sounds were regular but muffled. No murmurs or friction rubs were heard.

A serologic test for syphilis was negative. Blood studies revealed a hematocrit of 52.8 per cent, sedimentation rate of 2 mm. per hour and white blood cell count of 6,950 per cu. mm. Differential count revealed 4 per cent juvenile neutrophils, 67 per cent segmented neutrophils, 23 per cent lymphocytes and 6 per cent monocytes. The icterus index was 8. The urine was free of abnormalities. X-ray examination disclosed a greatly enlarged cardiac shadow with a globular configuration. (Fig. 5.) The lung fields were clear. On fluoroscopy the cardiac pulsations appeared to be almost entirely absent.

The patient was admitted to The Johns Hopkins Hospital. Further studies showed that the stool was guaiac-negative, an electrocardiogram was essentially normal, the serum cholesterol was 190 mg. per 100 ml. and the old tuberculin reaction test was negative up to a dilution of 1:100.

On May 28, 1954, a pericardial tap was performed and approximately 200 ml. of golden brown opalescent fluid was removed. No cholesterol crystals were noted. The fluid had 9,170 erythrocytes per cu. mm. and 460 white cells per cu. mm., with 59 per cent mononuclear cells and 31 per cent polymorphonuclear cells. The venous pressure before the procedure was 100 mm. of water and not changed by the tap. Circulation time was thirteen seconds (Decholin). The fluid was examined for acid-fast bacilli and cultured on routine media. All these studies were negative. Chemical studies of the pericardial fluid revealed the non-protein nitrogen to be 29 mg. per 100 ml., sugar 108 mg. per 100 ml., cholesterol 122 mg. per 100 ml., albumin 4.2 gm. and globulin 1.3 gm. per 100 ml.

The patient was asymptomatic throughout his hospital stay. Careful x-ray studies, including laminagrams, were performed and there was noted to be a ring of radiolucency within the dense cardiac shadow. This was believed to represent a thickened epicardial fat pad which was visualized on the x-ray film because of its lighter density as compared to the fluid surrounding the heart itself [*1*]. During the course of the patient's hospitalization considerable attention was directed to the unusual appearance of his eye grounds. The patient was seen in consultation by Dr. William Tillet, Jr., who stated that the retinal arterial changes might be congenital but were certainly abnormal. During the course of the patient's hospitalization his blood pressure was noted to be variable, with one or two readings as high as 190/100 mm. Hg but usually in the neighborhood of 140/90 mm. Hg. The patient was discharged on June 4, 1954, with a diagnosis of "pericardial effusion of unknown etiology."

The patient was permitted to return to light work. He has been seen periodically since that time and has remained entirely well. His weight remains about 210 pounds. His blood pressure has varied between 130/80 mm. Hg and 110/70 mm. Hg. The unusual pattern of blushing has persisted as has the unusual tortuosity of the blood vessels in his optic fundi. His cardiac dullness remains greatly enlarged both to the right and left without any significant change in the over-all cardiac size on repeated examination up to January 22, 1957, when the patient was last seen. An electrocardiogram on this occasion again revealed a normal record. In view of his absence of symptoms and good general health, it has not been considered advisable to risk repeated pericardial aspiration. He is performing his regular occupation.

Following the appearance of the second case of pericarditis approximately three years after the first case had been observed, an attempt was made to examine as many members of the family as was possible. In the autumn of 1954 it was possible to obtain chest x-ray films on five of the remaining six siblings; these were all entirely negative. Red blood cell counts and hematocrit determinations were performed and no other instance of polycythemia was noted. Two of the brothers and one of the sisters were available for examination of the optic fundi and except for slight tortuosity of the arterioles in the twenty-eight year old sister and very slight arterial compression without tortuosity in the thirty-seven year old brother no

other abnormalities were noted. Diabetes had developed in the father in 1956.

As far as is known the patients' ancestry is English and Irish. The maternal grandmother was known to have had diabetes. The paternal grandmother died of pneumonia at the age of seventy-five.

COMMENTS

Many questions posed by these cases remain unanswered. It is impossible to establish the duration of the disease in either brother. Quite conceivably, the second patient (W. Y.) may have been affected at the same time as his younger brother, despite the history that a chest x-ray film was "negative" in 1952. Since more than three years have elapsed since he came to our attention and there has been no change in his condition, it does not strain one's belief to suppose that his pericarditis may have existed for at least an equal span of time prior to its recognition. Similarly, the first patient may have had a pericardial effusion for some time prior to the survey x-ray examination.

The polycythemia which was noted in the younger brother remains a puzzle. The usual causes of this condition were considered but no evidence for these could be found. Polycythemia is not considered to be a feature of pericardial effusion of the usual types.

The tortuosity of the retinal arterioles and the peculiar erythematous flush which were noted in the second case probably are familial constitutional anomalies. It is a matter of speculation as to whether these features bear any relationship to the pericarditis.

Many diagnostic studies were made but no evidences for such conditions as tuberculosis, fungus infection, tumor, cysts, collagen disease or thyroid disease were found. The fluid in both patients showed remarkably little indication of inflammatory cellular reaction. The possibility that both brothers were victims of hemorrhagic effusions with resorption of blood seems unreasonably far-fetched. Even the resected specimen of pericardium in the first patient provided no clue as to the possible etiology of the pericardial effusions. The round cell foci are quite a non-specific finding and these foci were mild and scattered.

Chylopericardium, an instance of which was reported by Madison and Logue recently [*2*], seems to be an entirely unrelated clinical entity.

A plausible possibility is that both brothers were afflicted with "benign idiopathic pericarditis," a disease of possible viral origin. It is well recognized that this may be a chronic and recurrent illness [*3–5*]. However, such a diagnosis can be made only by exclusion, and many of the reported cases may represent other kinds of pericardial disease. It is worth considering that these brothers may represent instances of a hitherto unknown hereditary disorder with vascular and hematopoietic disturbances in addition to pericardial effusion. At present there is no reasonable basis upon which to relate these features. Family investigations of instances of chronic pericardial effusion might be worth pursuing.

The discovery of cholesterol crystals in our first patient prompted a survey of previously reported cases of "cholesterol pericarditis." Effusions containing crystals of cholesterol are, of course, well known in tuberculosis of the pleura. The literature on "cholesterol pericarditis" contains instances of tuberculosis [*6*], neoplasm [*7*], thyroid insufficiency [*8,9*], chronic hemorrhage [*10*] and cases without known cause [*11,12*]. It is clear, then, that "cholesterol pericarditis" is not a primary single disorder. Explanations for the appearance of crystalline cholesterol in serous fluids have been sought by most of the authors who have reported cases. The most likely hypothesis depends on the fact that absorption from the pericardial surfaces is quite slow. Under such circumstances deposition of free crystalline cholesterol may be the end result of disruption of soluble lipoprotein macromolecules over a long period of time. Similar notions have been offered to account for deposition of cholesterol in the intimal layers of arterial walls.

Our first patient had cholesterol crystals only in the first three aspirates. Subsequent taps were free of crystals. This would be in accord with the concept that a very slow degradation of lipoprotein complexes is necessary for crystals to appear.

The patients reported by Creech [*12*] and by Ada [*11*] are of great interest since the more usual kinds of chronic pericarditis seemed to be reasonably well excluded by their studies. Unlike our two brothers, symptoms of pericarditis were quite striking.

Ada's patient, a twenty-seven year old woman, had experienced shortness of breath, fatigue and chest pain, and was noted to have signs of heart failure. The fluid which was described was quite similar to that removed from our patient with

respect to its appearance, the paucity of cells, the relatively normal total cholesterol content and the large phagocytic cells with fat globules. At operation her pericardium was noted to be thickened, and pathologic study revealed some granulation tissue with small numbers of inflammatory cells, a poorly preserved mesothelium and replacement of the fibers of the pericardium by a mass of cholesterol crystals and large numbers of foreign body giant cells. Only slight infiltration with polymorphonuclear leukocytes and lymphocytes was noted.

Creech's patient had become ill with chest pain, epigastric tenderness and fever. At exploration he was noted to have a constrictive pericarditis with a pericardium of varying thickness. Microscopic examination revealed hyaline connective tissue which was focally infiltrated with lymphocytes, plasma cells and large mononuclear cells, with occasional aggregations of lymphocytes. A few slit-like cholesterol clefts were noted. Foam cells and giant cells were present. One of the original fluid specimens was said to show tubercle bacilli, so this case may represent an unusual type of tuberculous pericarditis. At least some doubt remains as to whether this is an instance of idiopathic "cholesterol" pericarditis.

SUMMARY

Two brothers with asymptomatic sterile chronic pericardial effusions are described. The first patient, who had cholesterol crystals in his fluid, has been followed up for over six years and, despite pericardiectomy, no explanation for his disease has been found. The second brother, found to have pericarditis three years after the first patient, was also symptom-free and has remained well for more than three years of observation. A peculiar vascular anomaly of the skin and eyegrounds was noted in this patient.

The usual causes of chronic pericarditis and "cholesterol" pericarditis were not found in these brothers. It is not known whether these cases represent a variety of benign idiopathic pericarditis or some complex heritable disorder.

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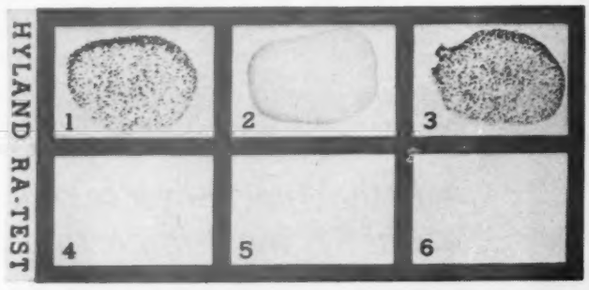
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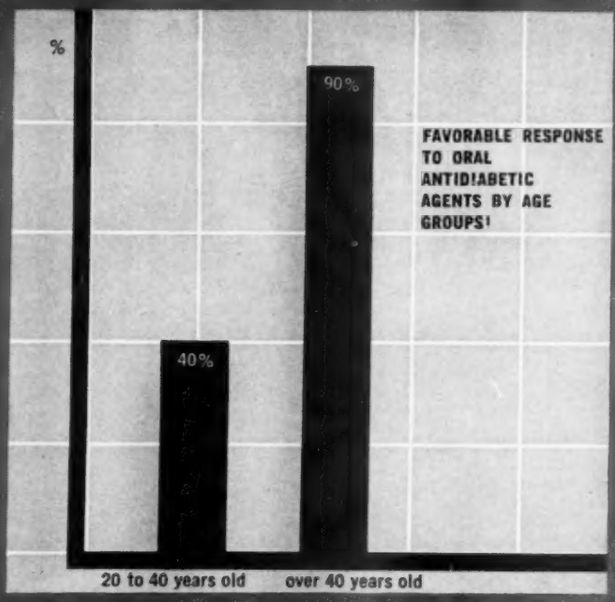
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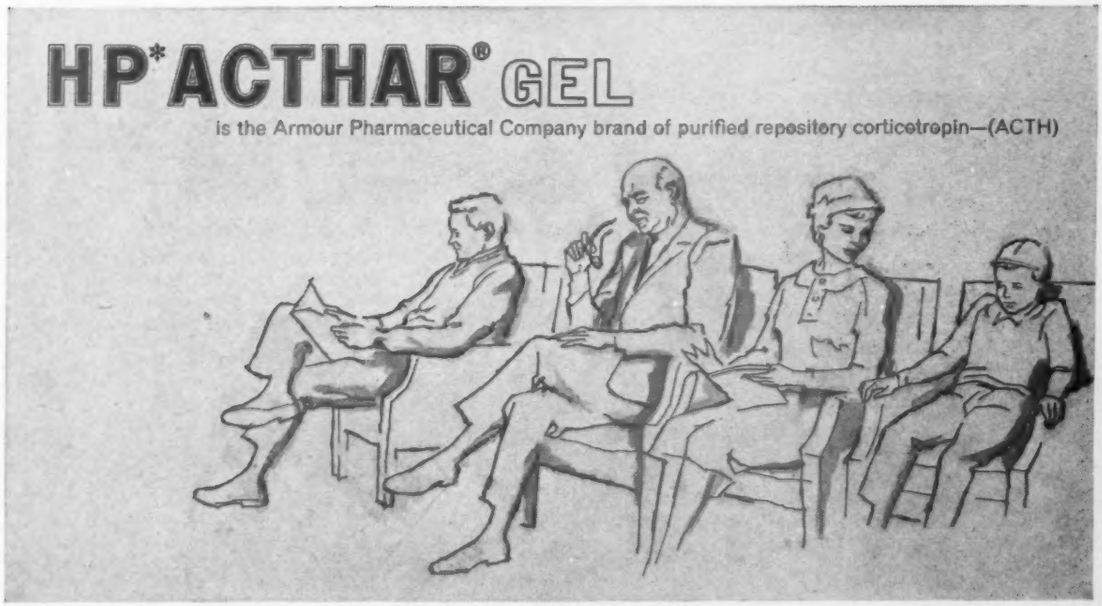
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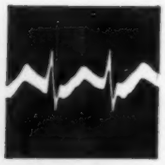


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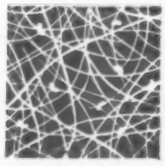
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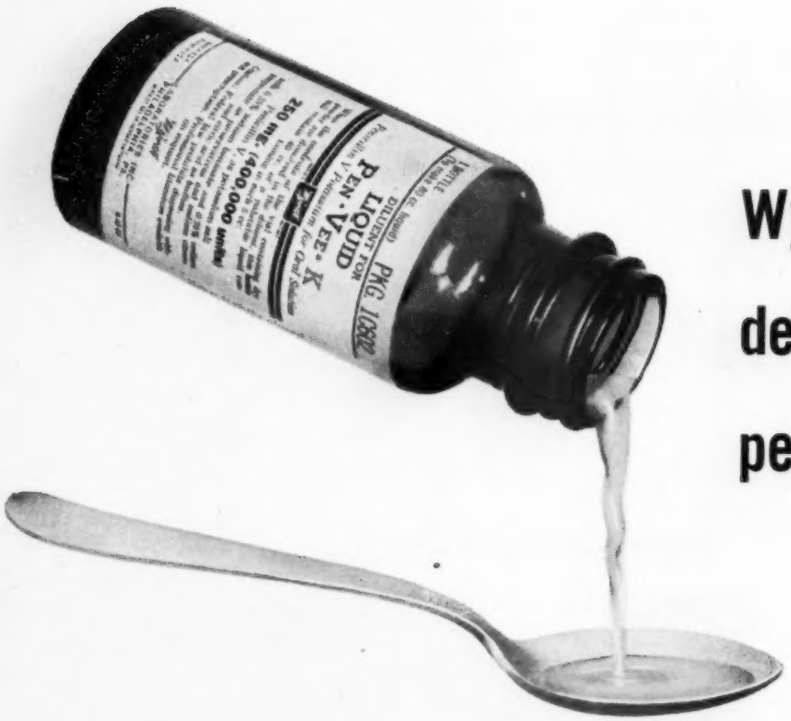
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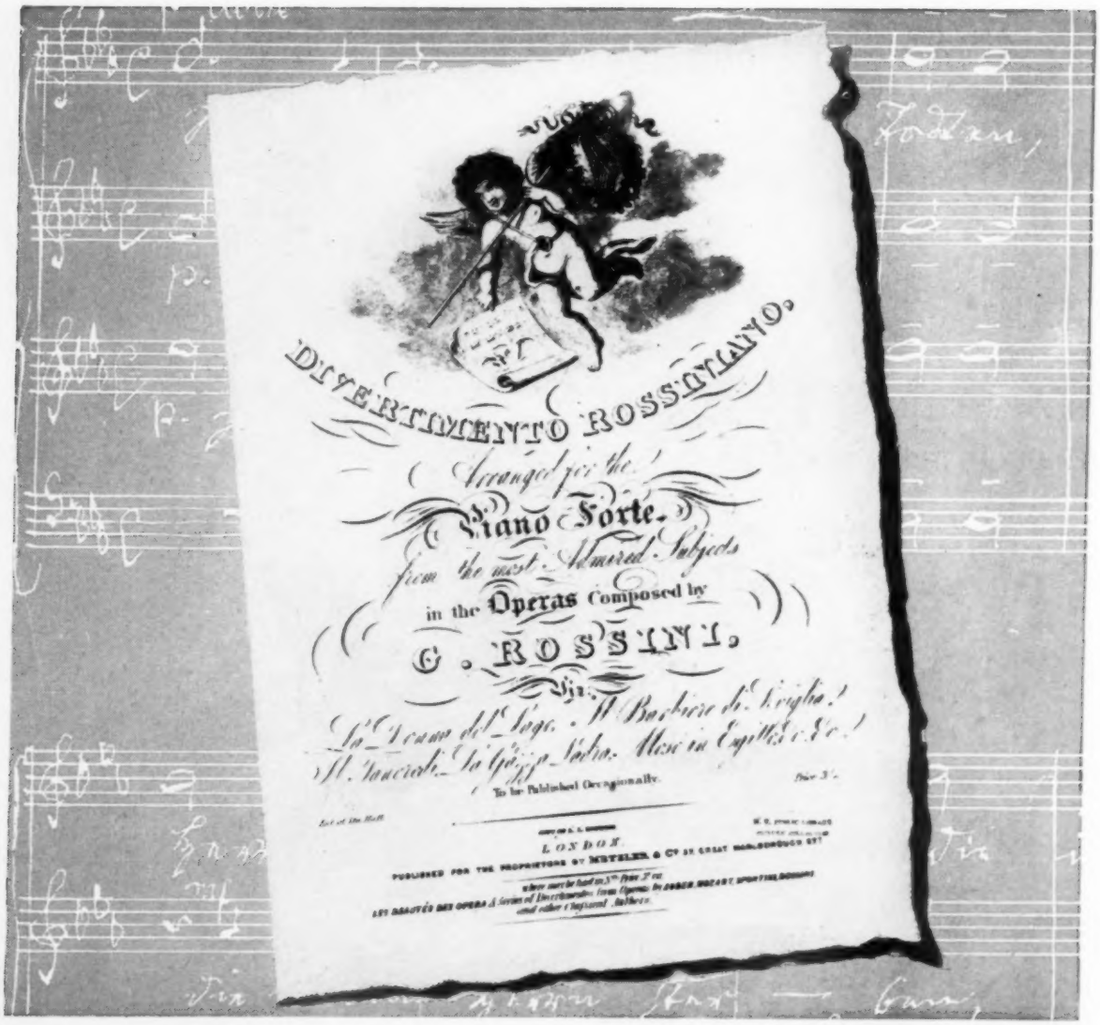
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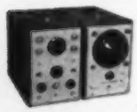
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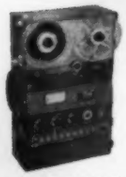
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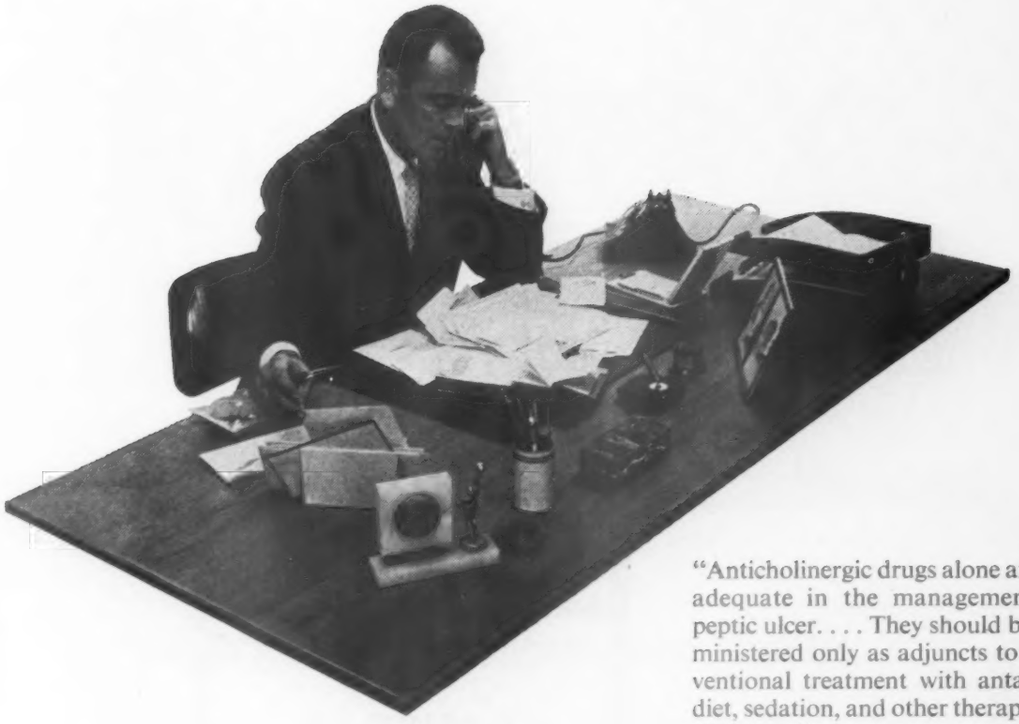
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"KENACORT" IS A SQUIBB TRADEMARK.

SQUIBB

CORT

Squibb Triamcinolone

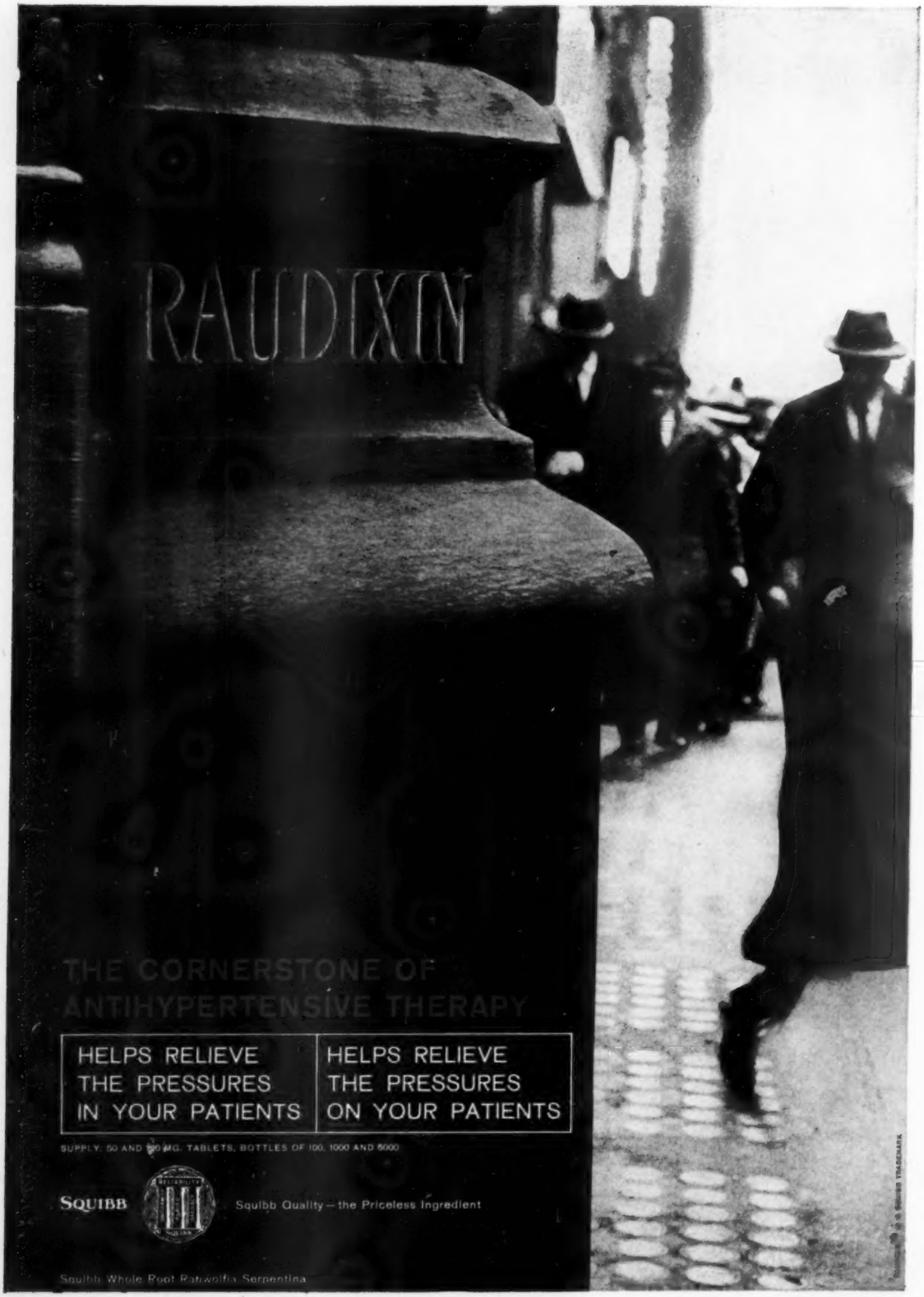


for all your patients with dermatoses requiring corticoids

Kenacort, particularly in treating inflammatory skin conditions, has also proved effective where other steroids have failed. It quickly alleviates itching, erythema, and irritation with its enhanced antiallergic, anti-inflammatory and antipruritic activity. Rapid clinical improvement is accomplished on a low dosage schedule[1-3] with few side effects to worry about.[1-5] (Kenacort is particularly valuable for your dermatologic patients with hypertension, cardiac disease, obesity and those prone to psychic disturbances.) Excellent results have been reported in treating localized neurodermatitis, contact and seborrheic dermatitis, alopecia areata, chronic eczematous eruptions — including atopy, and many cases of psoriasis.[3] Because of its relative freedom from untoward reactions, Kenacort provides corticosteroid benefits to many patients who until now have been difficult to control.

SUPPLIED:
Scored tablets of 1 mg. — Bottles of 50
Scored tablets of 2 mg. — Bottles of 50
Scored tablets of 4 mg. — Bottles of 30 and 100

Squibb Quality — the Priceless Ingredient


RAUDIXIN
THE CORNERSTONE OF
ANTIHYPERTENSIVE THERAPY
HELPS RELIEVE
THE PRESSURES
IN YOUR PATIENTS
HELPS RELIEVE
THE PRESSURES
ON YOUR PATIENTS
SUPPLY: 50 AND 100 MG. TABLETS, BOTTLES OF 100, 1000 AND 5000
SQUIBB
Squibb Quality—the Priceless Ingredient
Squibb Whole Root Rauwolfia Serpentina

in skin disorders

Decadron*

DEXAMETHASONE

treats more patients more effectively
a new order of magnitude in corticosteroid effectiveness
a new order of magnitude in margin of safety

Striking clinical results with DECADRON are reported† in 92 percent of 319 patients with dermatological disorders, including cases previously unresponsive or resistant to corticosteroids. There were no major complications, and even minor side effects occurred in less than eight percent of patients.

Moreover, in many cases reactions induced by previous steroid therapy, such as edema, Cushingoid appearance, headache, vertigo, muscular weakness, depression, hirsutism, and glycosuria, **disappeared during therapy with DECADRON.**

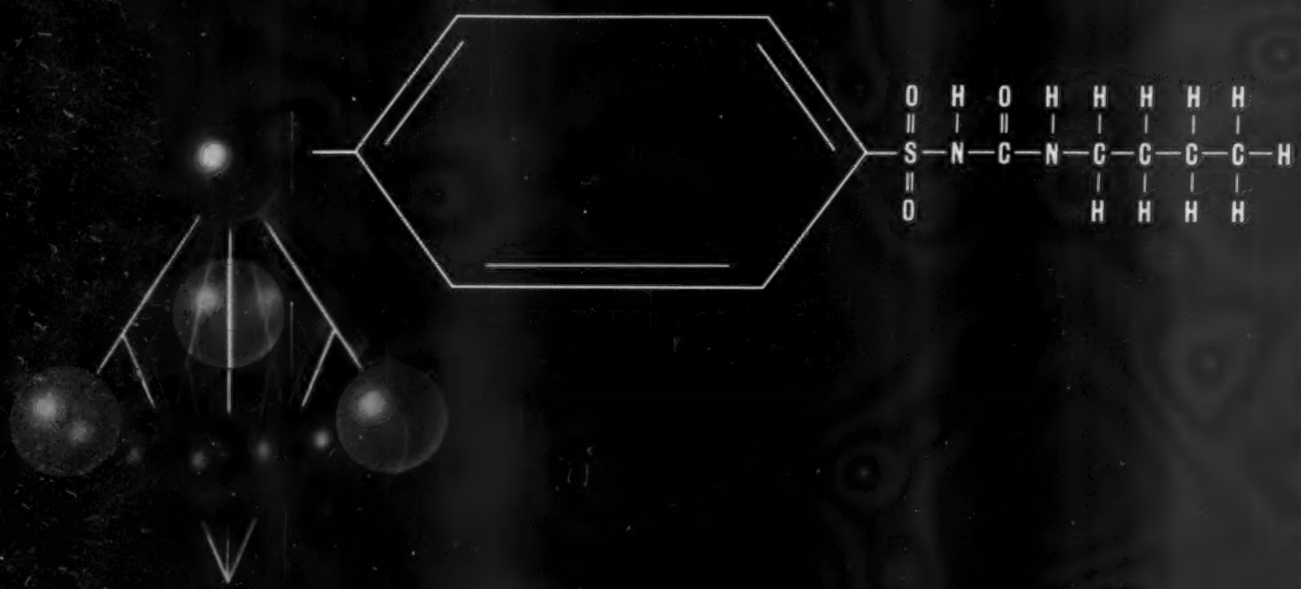
†Analysis of clinical reports.

Dosage: One 0.75 mg. tablet of DECADRON will usually replace one 4 mg. tablet of methylprednisolone or triamcinolone, one 5 mg. tablet of prednisone or prednisolone, one 20 mg. tablet of hydrocortisone, or one 25 mg. tablet of cortisone.

Supplied: As 0.75 mg. and 0.5 mg. scored, pentagon-shaped tablets in bottles of 100 and 1000.

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An exclusive

methyl "governor" prevents hypoglycemia ...makes Orinase* a true euglycemic agent

The significant difference between Orinase and all other antidiabetes agents is that there is virtually no danger of hypoglycemic reactions as a result of Orinase therapy, regardless of dosage.

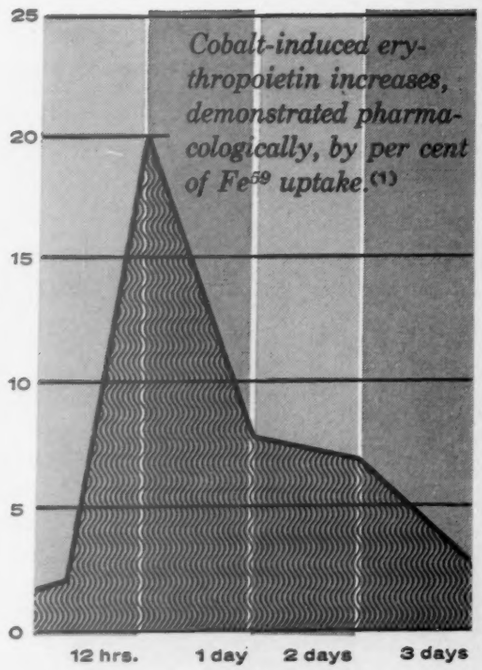
A logical explanation is that Orinase's exclusive methyl group in the para position serves as a "governor" to prevent hypoglycemia by facilitating the rapid inactivation of the molecule in the body. There is no *cumulative* effect.

The result is that, in patients in whom maintenance dosage has been established, Orinase lowers the blood sugar *to* normal levels, but almost never *beyond* that point. In other words, Orinase is a true *eu*glycemic agent, in contradistinction to the others, which actually *are* hypoglycemic agents.

This unique margin of safety is especially important in the patient requiring insulin, because Orinase, superimposed on his insulin dosage, constitutes no added danger of hypoglycemia. This makes it feasible for you to smooth out the "peaks and valleys" of erratic blood sugar levels . . . to "stabilize" a surprising percentage of labile diabetics.

*TRADEMARK, REG. U. S. PAT. OFF.—TOLBUTAMIDE, UPJOHN

Upjohn *The Upjohn Company, Kalamazoo, Michigan*



Activates the physiologic mechanism in anemia therapy

RONCOVITE®-mf

Each tablet contains: Cobalt chloride (Cobalt as Co..3.7 mg.)..15 mg., Ferrous Sulfate, exsiccated..100 mg.

Only cobalt among therapeutic agents enhances production of erythropoietin to promote red cell formation.[1,2,3]

With Roncovite-MF, increased erythropoietin production permits excellent hematopoietic response with sharply reduced iron dosage.

Cobalt-iron (Roncovite therapy) has been demonstrated as superior to iron alone in the common hypochromic anemias such as menstrual anemia, anemia of pregnancy, nutritional anemia of infancy and refractory anemias of chronic infection.[4,5,6,7,8]

(1) Goldwasser, E.; Jacobson, L. O.; Fried, W., and Pizak, L. F.: Blood 13:55 (Jan.) 1958. (2) Gurney, C. W.: Jacobson, L. O. and Goldwasser, E.: Ann. Int. Med. 49:363 (Aug.) 1958. (3) Korst, D. R.; Bishop, R. C. and Bethell, F. H.: J. Lab. & Clin. Med. 52:364 (Sept.) 1958. (4) Ausman, D. C.: Journal-Lancet 76:290 (Oct.) 1956. (5) Holly, R. G.: Obst. & Gynec. 9:299 (Mar.) 1957. (6) Holly, R. G.: Clin. Obst. & Gynec. 1:15 (Mar.) 1958. (7) Diamond, E. F.; Gonzales, F., and Pisani, A.: Illinois M. J. 113:154 (April) 1958. (8) Hill, J. M.; La Jous, J., and Sebastian, F. J.: Texas State J. Med. 51:686 (Oct.) 1955.

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remember
this name



SQUIBB

Squibb Quality - the Priceless Ingredient

*RAUTRAX IS A SQUIBB TRADEMARK.



House call: agitation

The acutely excited patient can be quickly calmed when SPARINE is on hand in the physician's bag. In both medical and mental emergencies, SPARINE quiets hyperactivity, encourages cooperation, and simplifies difficult management.

SPARINE gives prompt control by parenteral injection and effective maintenance by the intramuscular or oral route. It is well tolerated.

Comprehensive literature supplied on request

Sparine® HYDROCHLORIDE

Promazine Hydrochloride, Wyeth

INJECTION TABLETS SYRUP

Wyeth®
Philadelphia 1, Pa.

PAIN Zactirin®

Ethoheptazine Citrate with Acetylsalicylic Acid, Wyeth

for everyday pain control . . .

for your many patients requiring potent analgesia but not an injected narcotic

Proved by extensive evaluation[1,2,3] in 1998 patients in diverse areas of medicine and surgery, including:

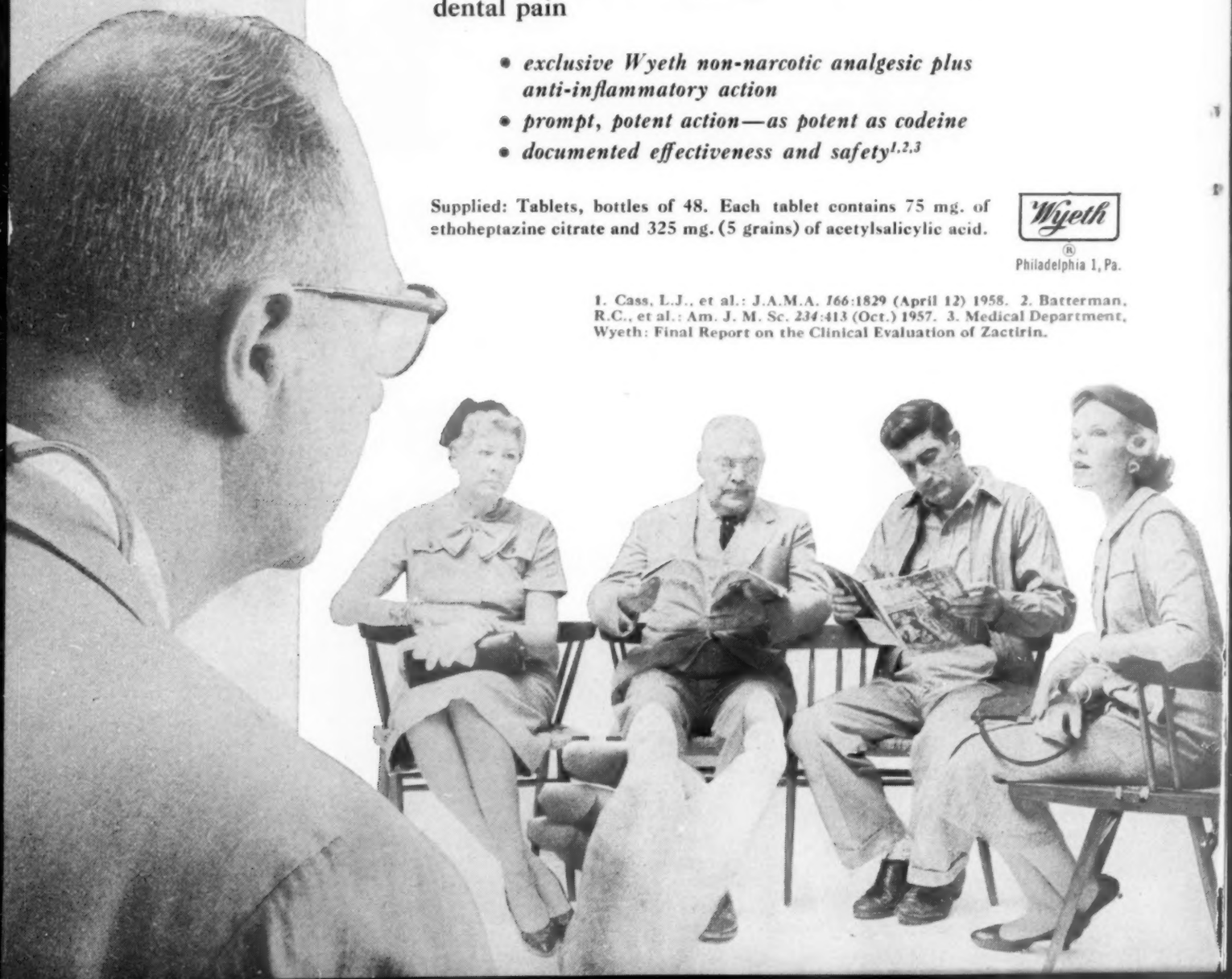
arthritis, bursitis, early metastatic carcinoma, fibrositis, grippe, herpes zoster, ligamental strain, low back pain, menstrual pain, myalgia, myositis, neuritis, pleurisy, postoperative pain, postpartum pain, sciatica, trauma, dental pain

- *exclusive Wyeth non-narcotic analgesic plus anti-inflammatory action*
- *prompt, potent action—as potent as codeine*
- *documented effectiveness and safety[1,2,3]*

Supplied: Tablets, bottles of 48. Each tablet contains 75 mg. of ethoheptazine citrate and 325 mg. (5 grains) of acetylsalicylic acid.

Wyeth®
Philadelphia 1, Pa.

1. Cass, L.J., et al.: J.A.M.A. *166*:1829 (April 12) 1958. 2. Batterman, R.C., et al.: Am. J. M. Sc. *234*:413 (Oct.) 1957. 3. Medical Department, Wyeth: Final Report on the Clinical Evaluation of Zactirin.



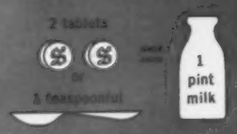
MILK-LIKE IS THE ACTION OF...

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UNIQUE ANTACID THAT "TITRATES LIKE MILK"

Its creamy, mint flavor is pleasing even to peptic ulcer patients who take it month after month. The unique, milk-like action of TITRALAC assures prompt, prolonged relief of hyperacidity without acid rebound or constipation.

IN BUFFERING POWER—



TITRALAC is effective in small doses. Two TITRALAC Tablets contain 0.36 Gm. glycine and 0.84 Gm. calcium carbonate. One teaspoonful TITRALAC Liquid approximates two tablets.

AND WITH A SPASMOLYTIC...

TITRALAC-SP

(TITRALAC formula + 0.5 mg homatropine methylbromide)
Tr.M. REG. U.S. PAT. OFF.



Schenlabs

SCHENLABS PHARMACEUTICALS, INC.
NEW YORK 1, N.Y.
Manufacturers of NEUTRAPEN®
for penicillin reactions. 93386

FOR THE CARDIAC CANDIDATE CAUGHT IN THE PRESSURE SQUEEZE

MODERIL

Brand of rescinnamine

AVOIDS THE THERAPEUTIC EXTREMES OF PREVIOUS RESERPINE AND RAUWOLFIA AGENTS



"DEPRESSION ACCOMPANIED BY ANXIETY...WAS NOT SEEN..."[1] WITH THIS NEW ALKALOID OF RAUWOLFIA. OTHER UNDESIRABLE RAUWOLFIA-RESERPINE REACTIONS ARE SELDOM ENCOUNTERED OR ARE MINOR IN DEGREE.[1-3] PRODUCES SIGNIFICANTLY MORE STABLE AND SUSTAINED CONTROL OF THE TENSION-HYPERTENSION COMPLEX.[4] HIGHER DOSAGES MAY BE EMPLOYED WHERE INDICATED, WITH CONTINUED EXCELLENT TOLERATION.[1-4] ALSO PREFERRED FOR THERAPY OF ACUTE ANXIETY STATES AND CHRONIC MENTAL DISORDERS.[4,5]

Supplied: MODERIL Tablets—yellow, scored 0.25 mg. oval tablets, bottles of 100 and 500; salmon, scored 0.5 mg. oval tablets, bottles of 100.

Dosage: The recommended initial dosage is 0.5 mg. twice daily for two weeks, with reduction thereafter to a minimum maintenance dosage of 0.25 mg. once daily. For greater hypotensive effect after initial period, increase dosage cautiously by 0.25 mg. daily up to a maximum daily dosage of 2.0 mg. Prescribe after meals.

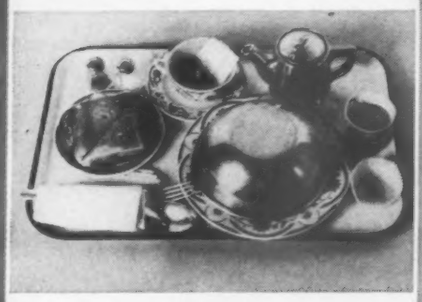
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Pfizer

PFIZER LABORATORIES
Division,
Chas. Pfizer & Co., Inc.
Brooklyn 6, New York







3 to make ready

ready to recover
ready to rebuild
ready to resist

That's the patient with the right form of VITERRA on his regimen! This comprehensive vitamin-mineral formula is ideal in frank nutritional deficiency states (VITERRA Therapeutic) or in daily supplementation (VITERRA Capsules, VITERRA Tastitabs® and VITERRA Pediatric).

VITERRA Therapeutic: when high potencies are indicated.

VITERRA Capsules: 10 vitamins, 11 minerals for balanced daily supplementation. Now in a soft, soluble capsule this small for added patient convenience.

VITERRA Tastitabs: VITERRA the way children like it best. Chew it, swallow it, let it melt in the mouth. Dissolve it in liquids, or add it to the formula.

Or prescribe convenient, delicious **VITERRA Pediatric** in the unique new Metered-Flow bottle.

Dosage: usually one capsule or Tastitab daily.

Supplied: CAPSULES: in 30's and 100's.
TASTITABS: bottles of 100.
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ROERIG Rx

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Division, Chas. Pfizer & Co., Inc.
Science for the World's Well-Being

NOW many more hypertensive patients may have THE FULL BENEFITS OF CORTICOSTEROID THERAPY

Except for one case of mild blood-pressure elevation (150/90) **no hypertension was seen in any of 1500 patients†** as a result of treatment with DECADRON—the new and, on a milligram basis, most potent of all corticosteroids. **Hypertension induced by other steroids diminished or disappeared.**

Thus with DECADRON, hypertension no longer appears to be a contraindication to successful corticosteroid therapy. And the dramatic therapeutic impact of DECADRON was virtually unmarred by diabetogenic or psychic reactions . . . Cushingoid effects were fewer and milder . . . and there were no new or "peculiar" side effects. Moreover, DECADRON helped restore a "natural" sense of well-being.

Decadron*

DEXAMETHASONE

treats more patients more effectively

†Analysis of clinical reports.

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DIARRHEAS! DYSENTERIES!

For more than 20 years, Pectin has been the key therapeutic ingredient of pharmaceutical specialties used specifically for the treatment of diarrheas, dysenteries and other intestinal disorders. As early as 1933, the detoxicating effect of Pectin was attributed to its galacturonic acid content.

PECTIN IN THE NAME IS NOT ENOUGH

Adequate dosage is essential. It is the galacturonic acid intake (2 to 4 grams of Pectin N.F. per day) that determines the effectiveness. In many instances the use of relatively inert adsorbent fillers has limited the amount of the therapeutic detoxicant, PECTIN, in the formulation to an inadequate dosage.

Exchange Brand Pectin N.F.

Increases bulk and fluid retention of upper intestinal contents and imparts a smooth, gelatinous consistency • Lubricates the intestinal wall • Promotes normal peristalsis without mechanical irritation • Reduces intestinal pH • Inhibits growth of many putrefactive and otherwise undesirable microorganisms in the intestines without affecting normal flora • Promotes assimilation of essential nutrients • Helps to conjugate and eliminate toxins • Reduces toxic side effects of therapeutic agents.

Exchange Brand Citrus Pectin and Pectin derivatives widely used in therapeutic specialties include:

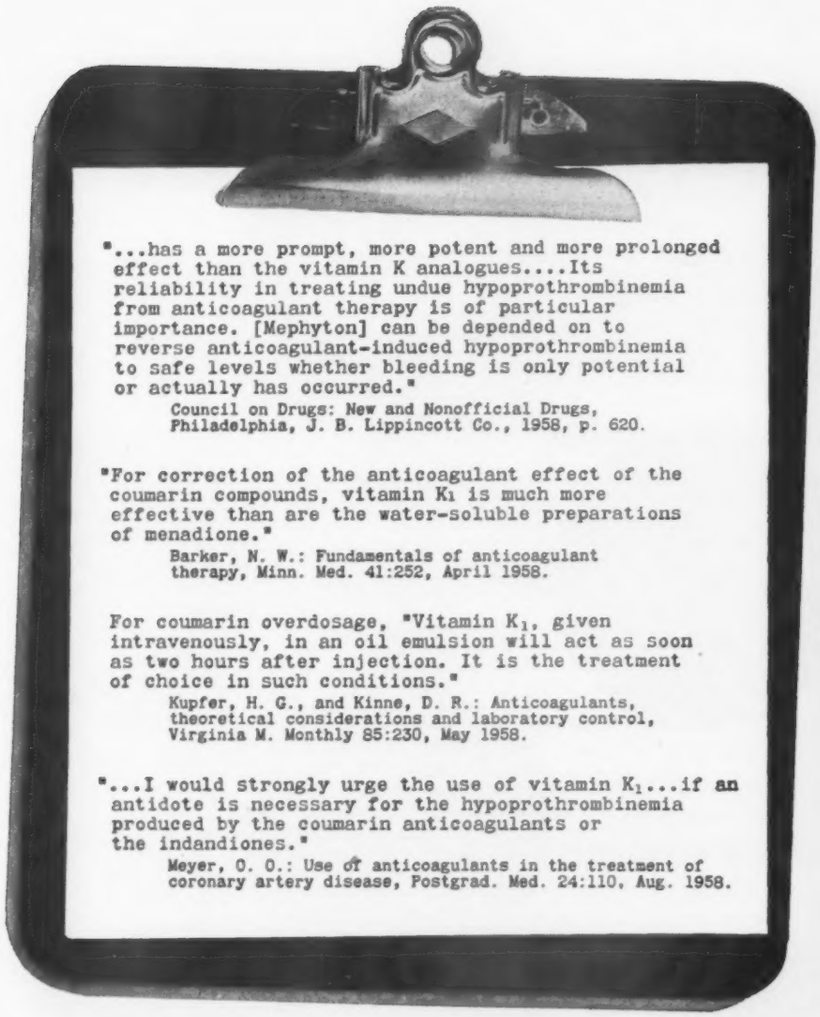
PECTIN N.F. • POLYGALACTURONIC ACID • PECTIN CELLULOSE COMPLEX • GALACTURONIC ACID • *These are available to the medical profession in specialties of leading pharmaceutical manufacturers.*

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PRODUCTS SALES DEPARTMENT
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ONTARIO, CALIFORNIA

Consensus:
The preferred antidote for anticoagulant-induced hypoprothrombinemia is 'Mephyton' (vitamin K_1).





chemically identical with naturally-occurring vitamin K_1

Mephyton®

Vitamin K_1

Dosage: Orally, to modify anticoagulant effects: 5 to 10 mg. initially; 15 to 25 mg. for more vigorous action. Intravenously, for anticoagulant-induced bleeding emergencies, 10 to 50 mg.; may be repeated as indicated by prothrombin time response. (Some clinicians advise their patients to keep a supply of tablets on hand at all times; if gross bleeding occurs, the patients are instructed to take 10 mg. and phone the doctor.)

Supplied: Tablets, 5 mg.; bottles of 100. Emulsion, each 1-cc. ampul contains 50 mg.; boxes of 6 ampuls.

MEPHYTON is a trademark of Merck & Co., Inc.

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in vaginitis

IMPROVED

TRICOFURON®

destroys all 3 *principal pathogens*

Whether vaginitis is caused by Trichomonas, Monilia or Hemophilus vaginalis—alone or combined—TRICOFURON IMPROVED swiftly relieves symptoms and malodor, and achieves a truly high percentage of cultural cures, frequently in 1 menstrual cycle. TRICOFURON IMPROVED provides: a *new* specific moniliacide MICOFUR® brand of nifuroxime, the *established* specific trichomonacide FUROXONE® brand of furazolidone and the *combined* actions of both against Hemophilus vaginalis.

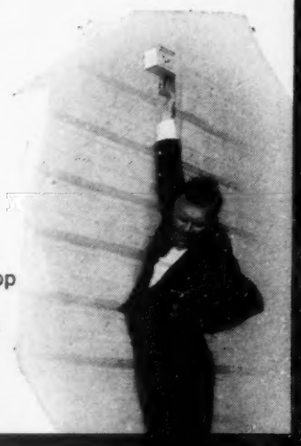
1. *Office* insufflation once weekly of the Powder (MICOFUR [*anti*-5-nitro-2-furaldoxime] 0.5% and FUROXONE 0.1% in an acidic water-soluble powder base). **2.** Continued *home* use twice daily, with the Suppositories (MICOFUR 0.375% and FUROXONE 0.25% in a water-miscible base).

℞ NEW BOX OF 24 SUPPOSITORIES WITH APPLICATOR FOR MORE PRACTICAL AND ECONOMICAL THERAPY.

NITROFURANS—a *new* class of antimicrobials—neither antibiotics nor sulfonamides.

EATON LABORATORIES, NORWICH, NEW YORK

REACHING FOR THOSE 9B's NEARLY PUT ME ON THE SHELF...



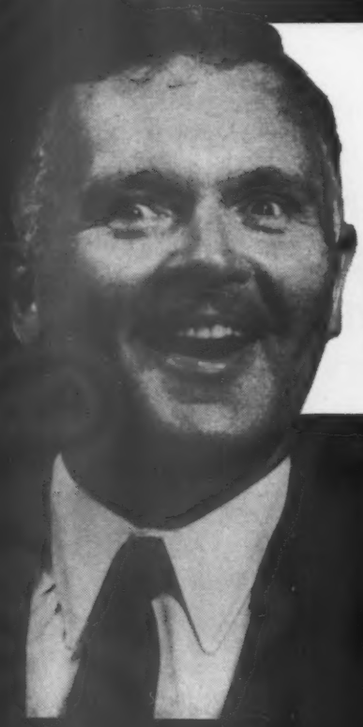
Reaching for 9B shoes and other top shelf sizes is no joke . . . it gave me a terrible kink in my back.



Before the day was over, I could hardly stoop to push a shoehorn.



I called my doctor that night and picked up the tablets he prescribed.



The pain went away fast—in just 15 minutes—and I was back on the job the next morning! But not one 9B customer came in the whole day!

Percodan®-Demi & Percodan® *Tablets*

Salts of Dihydrohydroxycodeinone and Homatropine, plus APC

FOR PAIN

ACTS FASTER — usually within 5-15 minutes. **LASTS LONGER** — usually 6 hours or more. **MORE THOROUGH RELIEF** — permits uninterrupted sleep through the night. **RARELY CONSTIPATES** — excellent for chronic or bedridden patients. **VERSATILE** — new "demi" strength permits dosage flexibility to meet each patient's specific needs. PERCODAN-DEMI provides the PERCODAN formula with one-half the amount of salts of dihydrohydroxycodeinone and homatropine.

AVERAGE ADULT DOSE: 1 tablet every 6 hours. May be habit-forming. Federal law permits oral prescription.

Each PERCODAN® Tablet contains 4.50 mg. dihydrohydroxycodeinone hydrochloride, 0.38 mg. dihydrohydroxycodeinone terephthalate, 0.38 mg. homatropine terephthalate, 224 mg. acetylsalicylic acid, 160 mg. phenacetin, and 32 mg. caffeine.

AND THE PAIN WENT AWAY FAST

Endo®

Literature? Write
ENDO LABORATORIES
Richmond Hill 18, New York

*U.S. Pat. 2,628,185

allergic SWELLING

(PARABROMDYLAMINE MALEATE) Dimetane® works

For your next patient with allergic swelling, itching or respiratory congestion associated with urticaria, Rx DIMETANE Extentabs® (12 mg.), Tablets (4 mg.), Elixir (2 mg./5 cc.) new DIMETANE-TEN Injectable (10 mg./cc.) or new DIMETANE-100 Injectable (100 mg./cc.).
A. H. Robins Co., Inc., Richmond 20, Virginia
Ethical Pharmaceuticals of Merit Since 1878

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STRESSCAPS®

STRESS FORMULA VITAMINS LEDERLE

for a more favorable therapeutic course

Host defense mechanism—fundamental to successful antibiotic control in severe infection—and recovery of normal organic function place a stress-demand on metabolic processes. Therapeutic supplements of B and C vitamins, as the basis of enzyme activity, protein-carbohydrate utilization, endocrine response and antibody formation,[1] are often required.[1,2]

STRESSCAPS provide high levels of water-soluble vitamins to insure a better prognosis.

Each capsule contains:

Thiamine Mononitrate (B_1)	10 mg.
Riboflavin (B_2)	10 mg.
Niacinamide	100 mg.
Ascorbic Acid (C)	300 mg.
Pyridoxine HCl (B_6)	2 mg.
Vitamin B_{12}	4 mcgm.
Folic Acid	1.5 mg.
Calcium Pantothenate	20 mg.
Vitamin K (Menadione)	2 mg.

Average dose: 1-2 capsules daily.

1. Daskal, H. M.: Antibiotic Med. & Clin. Ther. 2:33 (June) 1956.
2. Pollack, H. and Halpern, S. L.: Therapeutic Nutrition, National Research Council, Washington, D. C., 1952.

Lederle LEDERLE LABORATORIES, a Division of AMERICAN CYANAMID COMPANY, Pearl River, N. Y.

The Value of Oatmeal Protein

in the Dietotherapy of Undernutrition

Following periods of catabolic stress—when rehabilitation by diet is especially important—many patients cannot tolerate certain high-nutrition foods, and frequently show an aversion to foods with high-fat content.

Under such circumstances the physician is faced with the problem of selecting nourishing foods which are easily digested and well tolerated. Each day's menu must be built from a variety of high-protein, high-nutrient foods which appeal even to jaded appetites.

Oatmeal is an outstanding source of natural nutrients well suited for debilitated patients. It ranks highest among whole-grain cereals in content of protein, thiamine, and phosphorus.

The oatmeal serving with milk provides high-quality protein, unimpaired in processing or preparation. It supplies the essential amino acids in proper proportions for biosynthesis, repair, and replenishment of tissue. Oatmeal also provides significant amounts of several B vitamins and minerals important to physiologic rehabilitation.

The smooth, semi-solid texture of oatmeal, the ease of its digestibility, its inviting warmth, and its delicious nut-like taste combine to make it an appealing dish to patients of all ages.

Quaker Oats and Mother's Oats, the two brands of oatmeal offered by The Quaker Oats Company, are identical. Both brands are available in the Quick (cooks in one minute) and the Old-Fashioned varieties which are of equal nutrient value.

The Quaker Oats Company
CHICAGO





Obedrin®

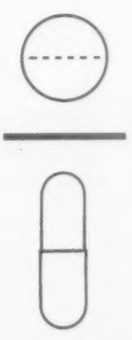
and the 60-10-70 Basic Plan

provide a rational weight control regimen

When the optimum weight is reached—the maintenance of desired eating patterns is most important. Continuing support by the physician is necessary. Here, Obedrin and the 60-10-70 Plan can be valuable aids to both the physician and patient.

FORMULA: *tablets and capsules*

Semoxydrine® HCl (Methamphetamine HCl)	5 mg.
Pentobarbital	20 mg.
Ascorbic Acid	100 mg.
Thiamine Mononitrate	0.5 mg.
Riboflavin	1 mg.
Nicotinic Acid	5 mg.



OBEDRIN PROVIDES:

- Methamphetamine for its proven anorexigenic and mood-lifting effects.
- Pentobarbital as a balancing agent, to guard against excitation.
- Vitamins B_1 and B_2 plus niacin to supplement the diet.
- Ascorbic acid to aid in the mobilization of tissue fluids.

Bristol, Tennessee • New York • Kansas City • San Francisco THE S. E. MASSENGILL COMPANY

for effective timing...a flexible dosage form

tablets or capsules



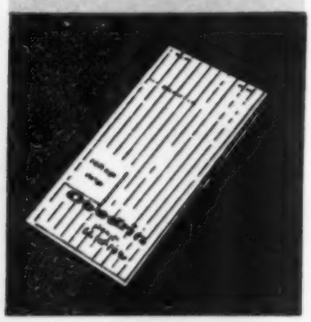
LUNCH DINNER EVENING SNACK

Obedrin tablets or capsules provide a flexible dosage form which may be prescribed to depress the appetite at peak hunger periods.

The pentobarbital content assures control of excess central nervous stimulation, and the 60-10-70 Basic Plan provides for a balanced food intake with sufficient protein and roughage.

Obedrin is available in tablet and capsule form.

Currently, mailings will be forwarded only at your request. Write for 60-10-70 menus, weight charts, and samples of Obedrin



ADVANTAGES OF OBEDRIN

- An effective anorexigenic agent
- A flexible dosage form
- Minimal central nervous stimulation
- Vitamins to supplement the diet
- No hazards of impaction

Obedrin®

and the 60-10-70 Basic Plan

Bristol, Tennessee • New York • Kansas City • San Francisco **THE S. E. MASSENGILL COMPANY**

for dramatic relief of penicillin reactions— early treatment with

NEUTRAPEN®

(NEUTRALIZES PENICILLIN) (Penicillinase Injectable,* SchenLabs)

the only specific for penicillin reactions

"Penicillinase [Neutrapen] should be given as soon as possible after onset of symptoms."[5]

(M. C. Zimmerman – Antibiotics Annual, 1957-58)

- effective in 97% of cases[1]
- acts within an hour, lasts up to a week[2,3]
- one injection sufficient in 80% of cases[1]
- itching abates promptly[4]
- most reactions clear in 12 to 96 hours[1,5]
- well tolerated[1-9]
- may be lifesaving in certain anaphylactoid reactions[6,7]



Obscure sources – even cases with no history of penicillin therapy respond to NEUTRAPEN if the reaction has been caused by penicillin from sources such as milk, Roquefort or Bleu cheese, or penicillin-containing vaccines.[1,5,9]

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References: (1) Zimmerman, M. C.: Clin. Med. *5*:305, 1958. (2) Becker, R. M.: New England J. Med. *254*:952, 1956. (3) Chen, J. Y. P.; Bard, J. W., and Balsito, A. A., in Welch, H., and Marti-Ibañez, F.: Antibiotics Annual 1957-1958, New York, Medical Encyclopedia, Inc., 1958, p. 321. (4) Minno, A. M., and Davis, G. M.: J.A.M.A. *165*:222 (Sept. 21), 1957. (5) Zimmerman, M. C., in Welch, H., and Marti-Ibañez, F.: Antibiotics Annual 1957-1958, New York, Medical Encyclopedia, Inc., 1958, p. 312. (6) Becker, R. M.: Ann. Int. Med. *48*:1228, 1958. (7) Becker, R. M., in Welch, H., and Marti-Ibañez, F.: Antibiotics Annual 1957-1958, New York, Medical Encyclopedia, Inc., 1958, p. 310. (8) Davis, G. M.: Discussion, Antibiotics Symposium, Washington, D. C., October 3, 1957. (9) Zimmerman, M. C.: J.A.M.A. *167*:1807 (Aug. 9), 1958.

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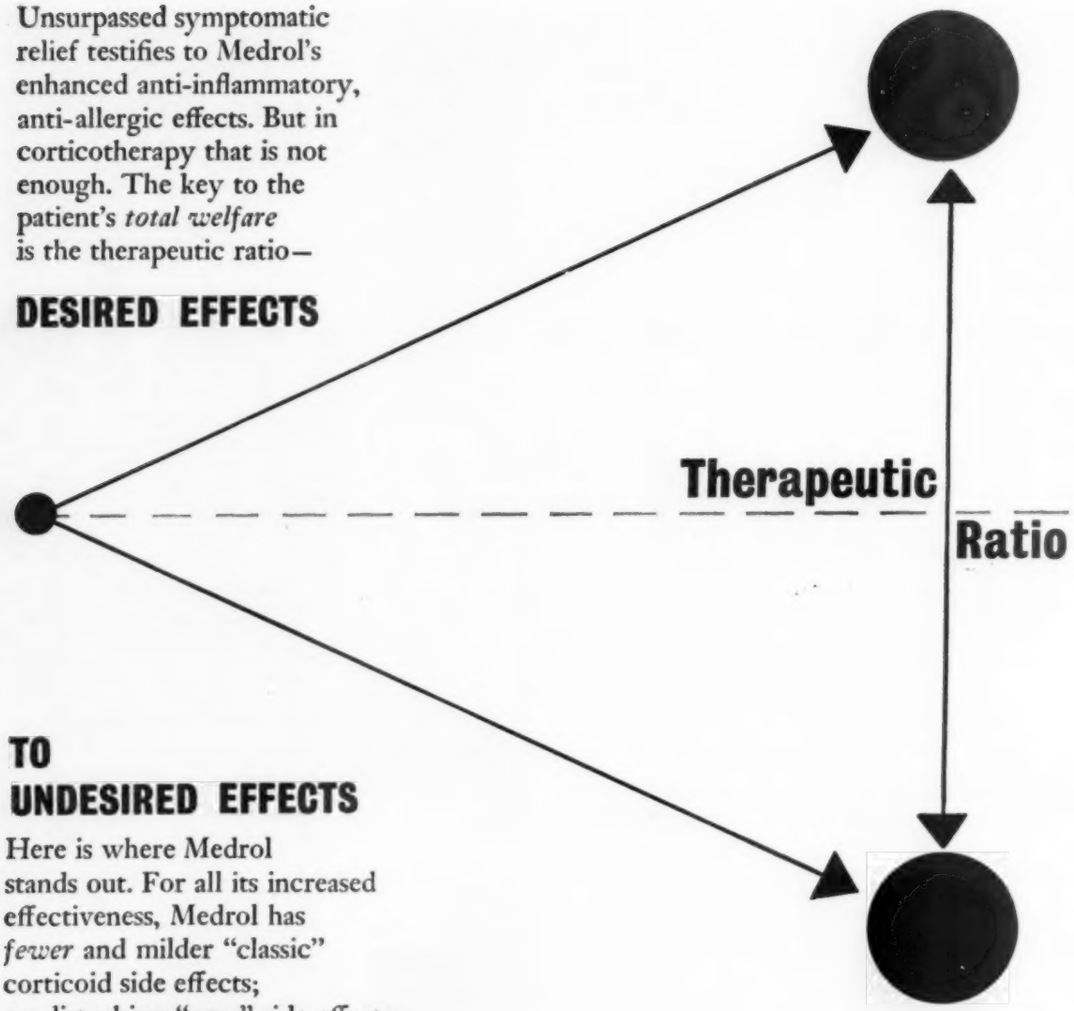
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Index to Advertisers

March, 1959

Abbott Laboratories . . . . . *Insert Facing Page* 48
American Sterilizer 58
Ames Company, Inc. 4, 80
Armour Pharmaceutical Company 81
Ayerst Laboratories 34–35, 16

Burroughs Wellcome & Co., Inc. 56, 63, 90

Ciba Pharmaceutical Products, Inc. . . . . 12–13–14–15, 65, *Fourth Cover*
Cyclotherapy, Inc. 121

Desitin Chemical Company 86

Eaton Laboratories 110
Endo Laboratories 111

Geigy Company 36

Hyland Laboratories 79

Irwin, Neisler & Co. 78

Lakeside Laboratories, Inc. 66
Lederle Laboratories Division, American Cyanamid Company 60–61, 76–77, 113
Thos. Leeming & Co., Inc. 48
Eli Lilly and Company 74
Lloyd Brothers, Inc. 99

The S. E. Massengill Company . . . . . *Insert Facing Page* 114
McNeil Laboratories, Inc. 51, 55
Mead Johnson 46
Merck Sharp & Dohme . . 29–30–31, *Insert Facing Page* 36, 42–43, 53, 62, 97, 106, 108–109, 119
Wm. S. Merrell Company 118–119

Organon Inc. 72

Parke, Davis & Company 70–71
Pfizer Laboratories, Division of Chas. Pfizer & Co., Inc. 57, 59, 104

Quaker Oats Company 114

Riker Laboratories, Inc. . . . . 67, 118, *Third Cover*
A. H. Robins Co., Inc. 112
Roche Laboratories, Div. of Hoffmann-La Roche Inc. 24, 32–33, 68–69, 87
J. R. Roerig & Co. 19–20–21, 105

Sanborn Company 88
Schenlabs Pharmaceuticals, Inc. 103, 117
G. D. Searle & Co. 75
Sherman Laboratories 54
E. R. Squibb & Sons, Division of Mathieson Chemical Corp. 6, 11, 17, 22, 44–45, 52, 82–83, 92, 93, 94–95, 96, 100
Sunkist Growers 107

The Upjohn Company 18, 98, 120

Wallace Laboratories 8, 41, 122, 124
Warner-Chilcott Laboratories 1
Winthrop Laboratories . . . . . 2, *Insert Facing Page* 24
Wyeth Laboratories 10, 23, 64, 73, 84–85, 89, 91, 101, 102

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